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Early use of non invasive ventilation in patients with amyotrophic lateral sclerosis: what benefits?

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Abstract. – OBJECTIVE: The aim of this study was to analyze the efficacy of an early start of NIV in ALS patients, evaluating respiratory and ventilatory parameters.

PATIENTS AND METHODS: Functional respiratory parameters and arterial blood gas analysis were evaluated in forty-six patients. All patients were informed about the benefits and possible adverse effects of therapeutic support with NIV and divided in two groups based on the compliance to early start therapy with NIV (Group A) or not (Group B).

RESULTS: Among 46 ALS patients consecutively visited in our Unit, we included 20 patients in the Group A and 16 in the Group B. We have emphasized the importance of the early use of NIV stressing the difference between two groups analyzed, particularly in terms of pulmonary function tests and arterial blood gas analysis. Significant correlation was observed between Vital Capacity (VC), Forced Expiratory volume in one second (FEV_1), and maximal inspiratory pressures (PImax).

CONCLUSIONS: Our study highlights the importance of noninvasive mechanical ventilation as a treatment for ALS patients and also shows the early start of NIV as an important approach in order to postpone the functional decline and the decrease of respiratory muscle strength.

Key Words:

Amyotrophic lateral sclerosis, Non invasive mechanical ventilation, Maximal inspiratory pressures, Forced expiratory volume in one second, Vital capacity, Hypercapnia.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurodegenerative disorder of unknown origin. Degeneration of spinal motor neurons is the main feature of the diseas. Motor nuclei of the lower brainstem and upper neurons of the motor cortex are often involved[1]. In general, survival does not exceed three years in 76% of cases and five to ten years in 8% to 16% of cases[2,3]. The gradual degeneration and death of motor neurons lead to death from respiratory insufficiency[4]. The guidelines of the European Federation of Neurological Societies (EFNS) and the American Academy of Neurology (AAN) recommend regular follow-up of symptoms and clinical signs of respiratory and ventilatory failure[5,6]. Evaluation of forced vital capacity (FVC) has been widely used as an important tool for the monitoring of pulmonary function in ALS patients. Anyway, the assessment of respiratory muscle strength by maximal inspiratory and expiratory pressures (PImax, PEmax), has become increasingly relevant in the early diagnosis of respiratory muscle weakness[7,8]. However, no single test is considered to be the most appropriate for detecting impending respiratory failure[9], because the presence of a restrictive ventilatory defect is characteristic, with reduced total lung capacity (TLC), normal or low functional residual capacity (FRC) and increased residual volume (RV), due to weakness of the expiratory muscles[6]. Although hypoxia with hypocapnia can be detected in an incipient phase, the typical finding is hypercapnia with a normal alveolar-arterial gradient, bicarbonate retention and increase in lactate. Non-invasive positive-pressure ventilation (NIV) and invasive mechanical ventilation (IMV) are used to alleviate respiratory symptoms, improve quality of life and prolong survival[5]. Therefore, respiratory function assessment is important for monitoring disease progression and determining the optimal timing for the initiation of NIV. NIV should be indicated in all neuromuscular patients with symptoms of res-

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piratory fatigue (orthopnoea) associated with functional respiratory dysfunction (drop in FVC/MIP) or symptoms of hypoventilation in the presence of hypercapnia or nocturnal desaturation[10].

The aim of our study was to analyze the efficacy of an early start of NIV in ALS patients, evaluating respiratory and ventilatory parameters.

Patients and Methods

From March to June 2014 we analyzed 46 patients (17 women and 29 men, mean age 63.7 ± 10.4 years) consecutively visited in our Respiratory Disease Unit (Policlinico Umberto I, Rome, Italy) suffering from ALS. Diagnosis of definite ALS was made when the following criteria were met[11]: (1) muscle weakness and atrophy in at least two noncontiguous muscle groups, lasting 6 months or longer; (2) pyramidal tract involvement; and (3) EMG evidence of diffuse impairment of the anterior horn cells. No patient had a time of diagnosis than 3 years and were excluded from the study patients with previous cerebrovascular events, arterial disease, ischemic heart disease, COPD, cancer. Other exclusion criteria were: the presence of an episode of acute respiratory failure (ARF) at the time of presentation requiring mechanical ventilation (MV); presence of a tracheotomy; inability to perform respiratory measurements. All patients underwent blood tests, evaluation of body mass index (BMI), calculated as weight (kg) divided by height squared (m^2), arterial blood gas analysis (ABG), measurement of systolic and diastolic blood pressure, ECGs, transthoracic echocardiography and pulmonary function tests (we specially focused on Vital Capacity, Forced Expiratory volume in one second (FEV_1), PImax and PEmax). Up visits were according to the patient's stability, every 30 days during 4 months (Time 0, Time 1, Time 2, Time 3, Time 4). Dynamic lung volumes and flow volume loops were assessed by means of a spirometer (Cosmed, Quark PFT, Pavona, Rome, Italy) which had measurement accuracy within 5% of volume. Technical procedures, acceptability and reproducibility criteria, interpretive values, standardization and equipment were in accordance with American Thoracic Society/European Respiratory Society recommendations[12]. All patients were informed about the benefits and possible adverse effects of therapeutic support with NIV and Cough Assist. Based on the compliance of each patient, we considered two groups:

- Group A: patients who started NIV from Time 0
- Group B: patients who refused NIV at Time 0 and subsequently started with the worsening of symptoms and signs

Adaptation to ventilation and adjustment of ventilator settings were always done during an inpatient admission. The type of ventilator and interface were selected based on the patient's comfort and adaptation, correction of gas-exchange abnormalities and the number of hours of ventilation. Equipment used included volumetric ventilator (PV 501, BREAS Medicals, Mölnlycke, Sweden) or pressure ventilator (BiPAP-ST30 "auto-trak" ventilator, Respironics Inc, Murrysville, PA, USA). Interfaces included custommolded and commercial nasal masks with chin-strap to minimize oral leaks.

All partecipants provided written informed consent and procedures complied with the standards of the Declaration of Helsinki.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD), and differences were evaluated by the paired Student *t* or Wilcoxon test, depending on the shape of the distribution curve. Categorical variables are expressed by count and percentage and compared by χ^2 or Fisher's exact test when appropriated.

The Spearman coefficient was used for measuring linear correlation between variables.

The probability values are 2-sided; a probability value < 0.05 was considered to indicate statistical significance.

Statistical analyses were performed by using software SigmaStat (San Josè, CA, USA). Power analysis was performed using STATA v.11 (College Station, TX, USA).

Results

Among 46 patients consecutively visited in our Respiratory Disease Unit, 7 were excluded for a medical history of cardiac disease (2 because of recent hospitalization for ischemic heart disease, 3 for the development of atrial fibrillation, 2 because of mitral valve prolapsed), 1 for severe renal failure and 2 patients suffering from

Table I. Patients demographics and clinical characteristics (data expressed as Mean ± Standard Deviation).

Variables	Totale (n = 36)	Group A (n = 20)	Group B (n = 16)	p
Gender: male (n. %)	58.3	60	56.25	NS
AGE (years)	63.7 ± 10.8	65 ± 9.34	62.18 ± 11	NS
Diagnosis: age (yrs)	61.8 ± 9.9	62.3 ± 9.65	61.18 ± 10.62	NS
BMI (kg/m^2)	25.79 ± 5.5	25.36 ± 4.63	26.32 ± 6.65	NS
SBP (mmHg)	70.83 ± 13.8	71.5 ± 13	70 ± 15	NS
DBP (mmHg)	128 ± 18.2	130 ± 17.9	125 ± 18.6	NS

BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

lung cancer. Thus 36 patients with ALS were included in our study and we included 20 patients in the Group A and 16 in the Group B.

Participants baseline characteristics are summarized in Table I. We did not show statistically significant differences between Group A and Group B for sex, current age, age at diagnosis, BMI and blood pressure.

The main clinical and instrumental parameters measured at Time 0 are shows in Table II.

All patients underwent transthoracic echocardiography with particular attention to the indices of pulmonary hypertension and right heart failure. The results showed no statistically significant differences observed between the two groups.

Among all the parameters investigated, we found that at the end of follow-up (Time 4), there is a worsening of the ventilatory capacity and arterial blood gas values in all patients, but, there was

Table II. Patients main clinical and instrumental parameters at Time 0 (data expressed as Mean ± Standard Deviation).

Variables	Group A (n = 20)	Group B (n = 16)	p
pH	7.40 ± 0.03	7.41 ± 0.05	–
pCO_2 (mmHg)	44.8 ± 5.12	45.43 ± 5.42	–
pO_2 (mmHg)	79.95 ± 8.59	78.06 ± 7.8	–
HCO_3^- (mmol/L)	28.9 ± 4	30.86 ± 4	–
SO_2 (%)	96.3 ± 2.6	95.5 ± 2.4	–
Lac (mmol/L)	1.4 ± 0.6	1.65 ± 0.8	–
FEV_1 (%)	60.6 ± 17.2	61.31 ± 13.95	–
FVC (%)	56.9 ± 11	61.37 ± 10.1	–
CV (%)	65.4 ± 10.8	62.93 ± 9.98	–
FEV_1/VC	88.27 ± 15.3	87.15 ± 19.86	–
PEF (%)	57.95 ± 18.6	57.37 ± 17.77	–
TLC (%)	84.65 ± 15.57	76.43 ± 24.32	–
DL_{CO} (%)	81 ± 18.64	75.08 ± 15.82	–
DL_{CO}/VA	100.83 ± 24.3	100.57 ± 17.34	–
PImax (cm H_2O)	36 ± 13.65	35 ± 14.87	–
PEmax (cm H_2O)	52.85 ± 16.9	54.37 ± 16.97	–
AHI	22.94 ± 14.2	22.98 ± 14.27	–
SO_2 minimum night (%)	83.97 ± 4.87	92.2 ± 1.69	–
SO_2 average night (%)	92.16 ± 2	84.49 ± 3.38	–
HR average night	70.3 ± 11	70.75 ± 10.2	–
EF (%)	47.75 ± 6.83	45.8 ± 7.87	–
PAP_S (mmHg)	37.25 ± 10	37.31 ± 9.4	–
TAPSE (mm/sec)	18 ± 4.42	17.37 ± 4.24	–
PVR (wood units)	3.11 ± 0.32	3.2 ± 0.28	–

PaO_2 = Partial pressure of oxygen; $PaCO_2$ = Carbon dioxide partial pressure; HCO_3^- = Bicarbonate ion; SO_2 = Oxygen saturation; Lac = Lactate; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; CV = Vital capacity; FEV_1/VC = Tiffenau index; PEF = Peak expiratory flow; TLC = Total lung capacity; DL_{CO} = Diffusing capacity for carbon monoxide; DL_{CO}/VA = Diffusing capacity for carbon monoxide/alveolar volume; PImax = Maximal inspiratory pressure; PEmax = Maximal expiratory pressure; AHI = Apnoea/hypopnoea index; HR = Hearth rate; EF = Ejection fraction; PAP_S = Pulmonary Artery Systolic Pressure; TAPSE = Tricuspid annular plane systolic excursion; PVR = Pulmonary vascular resistance.

a statistically significant difference with regard to FEV_1, FVC, Tiffenau Index (FEV_1 /VC), PImax, PEmax and Total Lung Capacity (TLC) (TLC especially at Time 3 and Time 4: 69.81% *vs*. 77.4 % $p < 0.02$; 55.9 *vs*. 62.8 $p < 0.007$, respectively), as summarized in Table III. We found a significant worsening of the Group B compared to Group A, especially regarding PImax, which showed a trend of decreased ability to reward: Time 1 (-28 cm H_2O *vs*. -34.1 cm H_2O $p < 0.05$), Time 2 (-25.18 *vs*. -31.45 cm H_2O $p < 0.04$), Time 3 (-21.56 cm H_2O *vs*. -27.3 cm H_2O $p < 0.03$), Time 4 (-18.18 *vs*. -24 cm H_2O $p < 0.007$). Similarly, we found a significant decrease of the PEmax from T2 (37.43 cm H_2O vs 44.85 cm H_2O, $p < 0.05$), then to T3 (30.75 cm H_2O *vs*. 38 cm H_2O, $p < 0.02$), up to T4 (27.43 cm H_2O *vs*. 35.9 cm H_2O, $p < 0.008$) (Figure 1). These results indicate that a decrease of inspiratory and expiratory muscle strength is actually the first negative predictive indicator of the worsening of the respiratory tract in ALS. In addition, we have shown that FVC had a decreasing trend from Time 0 to Time 2 but we found a difference between Group A and Group B in Time 3 and in Time 4 (43.56% *vs*. 47.9%, $p < 0.04$; 38.6% *vs*. 43.5%, $p < 0.02$, respectively). We not found differences between two groups about FEV_1 at Time 0, however at Time 2 (45.15% *vs*. 51%, $p < 0.05$), Time 3 (43.93% *vs*. 47.35%, $p < 0.05$) and Time 4 (39.8% *vs*. 44.8% $p < 0.05$) we have shown significantly lower values for Group B respect to Group A (Figure 2). These data show that the lung function of Group A were better than the Group B during the follow-up. This finding might be due to the use of timely treatment with NIV by the Group A, which would be reduced as much possible the respiratory muscles fatigue. All patients underwent ABG and the comparison between two groups at Time 0 and Time 1, shows that Group B had values of pH, pCO_2, HCO_3^- and lactate (Lac) worst of Group A (7.34 *vs*. 7.39, $p < 0.003$; 55.75 mmHg *vs*. 49.25 mmHg, $p < 0.001$; 40.27 mmol/L *vs*. 33.27 mmol/L, $p < 0.001$; 2.63 mmol/L *vs*. 1.93 mmol/L, $p < 0.002$ respectively). This assessment, carried out at each visit, showed a significant difference between the two groups even at T2, about pH, pCO_2, HCO_3^- and Lac (7.33 *vs*. 7.37, $p < 0.001$; 60.6 mmHg *vs*. 51.4 mmHg, $p < 0.001$; 45.7 mmol/L *vs*. 41.5 mmol/L, $p < 0.02$; 2.86 mmol/L *vs*. 2.26 mmol/L, $p < 0.006$ respectively). We found statistically significant reduction in the pH difference even at Time 3 (7.35 *vs*. 7.37, $p < 0.001$) and an increase in the pCO_2 at both Time 3 and Time 4 (59 mmHg *vs*. 53.8 mmHg, $p < 0.001$ and 55.8 mmHg *vs*. 58.6 mmHg, $p < 0.02$). During the assessment within 60 days (T2), we found a significant decrease in pO_2 and SO_2 in Group B (52 mmHg *vs*. 63.2, $p <$

Table III. Ventilatory parametrs and arterial blood gas values a T0 e a T4 (data expressed as Mean ± Standard Deviation).

Variables	Gruppo A (T0)	Gruppo B (T0)	p	Gruppo A (T4)	Gruppo B (T4)	p
pH	7.40 ± 0.03	7.41 ± 0.05	–	7.35 ± 0.04	7.36 ± 0.03	0.11
pCO_2 (mmHg)	44.8 ± 5.12	45.43 ± 5.42	–	55.6 ± 4.53	58.31 ± 3.19	0.02
pO_2 (mmHg)	79.95 ± 8.59	78.06 ± 7.8	–	59.3 ± 3.57	60.75 ± 4.42	0.14
HCO_3^- (mmol/L)	28.9 ± 4	30.86 ± 4	–	50.9 ± 5.28	53.11 ± 5.5	0.11
SO_2 (%)	96.3 ± 2.6	95.5 ± 2.4	–	91.6 ± 1.5	91.4 ± 2.08	0.36
Lac (mmol/L)	1.4 ± 0.6	1.65 ± 0.8	–	3 ± 0.36	3.2 ± 0.31	0.17
FEV_1 (%)	60.6 ± 17.2	61.31 ± 13.95	–	44.8 ± 11.3	39.87 ± 9.74	0.05
FVC (%)	56.9 ± 11	61.37 ± 10.1	–	43.35 ± 7.78	38.6 ± 5	0.02
CV (%)	65.4 ± 10.8	62.93 ± 9.98	–	44.5 ± 5.97	42.5 ± 5.7	0.5
FEV_1/VC	88.27 ± 15.3	87.15 ± 19.86	–	109.72 ± 9.61	116.75 ± 12.74	0.03
PEF (%)	57.95 ± 18.6	57.37 ± 17.77	–	44.45 ± 11.43	41 ± 10.7	0.18
TLC (%)	84.65 ± 15.57	76.43 ± 24.32	–	62.8 ± 7.83	55.93 ± 8	0.007
DL_{CO} (%)	81 ± 18.64	75.08 ± 15.82	–	58.14 ± 11.32	55.74 ± 8.86	0.24
DL_{CO}/VA	100.83 ± 24.3	100.57 ± 17.34	–	125.58 ± 15	131.9 ± 16.46	0.057
PImax (cm H_2O)	36 ± 13.65	35 ± 14.87	–	29.4 ± 8.58	18.18 ± 6.65	0.007
PEmax (cm H_2O)	52.85 ± 16.9	54.37 ± 16.97	–	35.9 ± 12.26	27.43 ± 6.35	0.008

PaO_2 = Partial pressure of oxygen; $PaCO_2$ = Carbon dioxide partial pressure; HCO_3^- = Bicarbonate ion; SO_2 = Oxygen saturation; Lac = Lactate; FEV_1 = Forced Expiratory Volume in one second FVC = Forced vital capacity; CV = Vital capacity; FEV_1/VC = Tiffenau index; PEF = Peak expiratory flow; TLC = Total lung capacity; DL_{CO} = Diffusing capacity for carbon monoxide; DL_{CO}/VA = Diffusing capacity for carbon monoxide/alveolar volume; PImax = Maximal inspiratory pressure; PEmax = Maximal expiratory pressure.

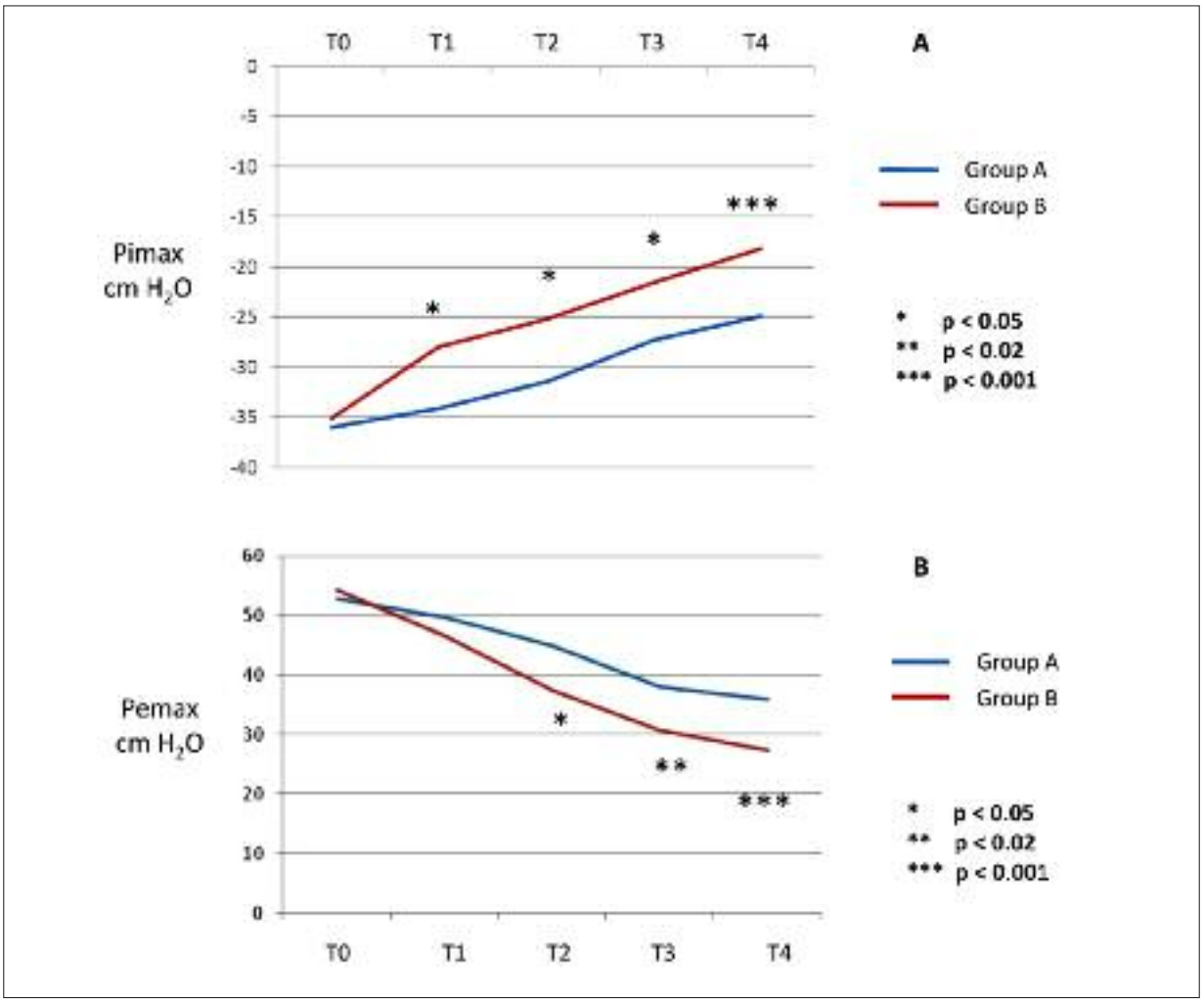

Figure 1. Trend of Maximal Inspiratory Pressure (PImax) ***(A)*** and Maximal expiratory pressure (PEmax) ***(B)*** in both groups.

0.001, 89.4% *vs*. 92.1%, $p < 0.001$, respectively). In fact, no patient included in this group has agreed to undergo therapy with the NIV at Time 0 and the worsening of arterial blood gas parameters occurred at the first control (T1), but not statistically significant. These outcomes show that the subsequent improvement of these parameters, up to T4, for the patients in Group B, it occurred at the beginning of the Non Invasive Mechanical Ventilation. However, to accept such treatment too late and only as a result of a worsening of symptoms and lung function, determined the necessity of the use of supplemental O_2 flows significantly higher than in Group A. The study of correlations, shows that there is an inverse relationship between the PImax and Vital Capacity at Time 0 and at Time 4, for all patients ($p < 0.05$, r -0.32, $p < 0.05$, r -0.44, respectively) (Figure 3). This finding was significant even between the PImax and the FEV_1, to Time 0 and Time 4 ($p < 0.05$, r -0.5, $p < 0.05$, r -0.61, respectively) (Figure 4). These results indicate that the deterioration of the PImax can be considered a negative predictor of increased muscle fatigue and, similarly, as the vital capacity (VC) and Forced Expiratory Volume in the first second (FEV_1), are indicators of the decline in lung function in patients with ALS.

Discussion

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of unknown origin, pro-

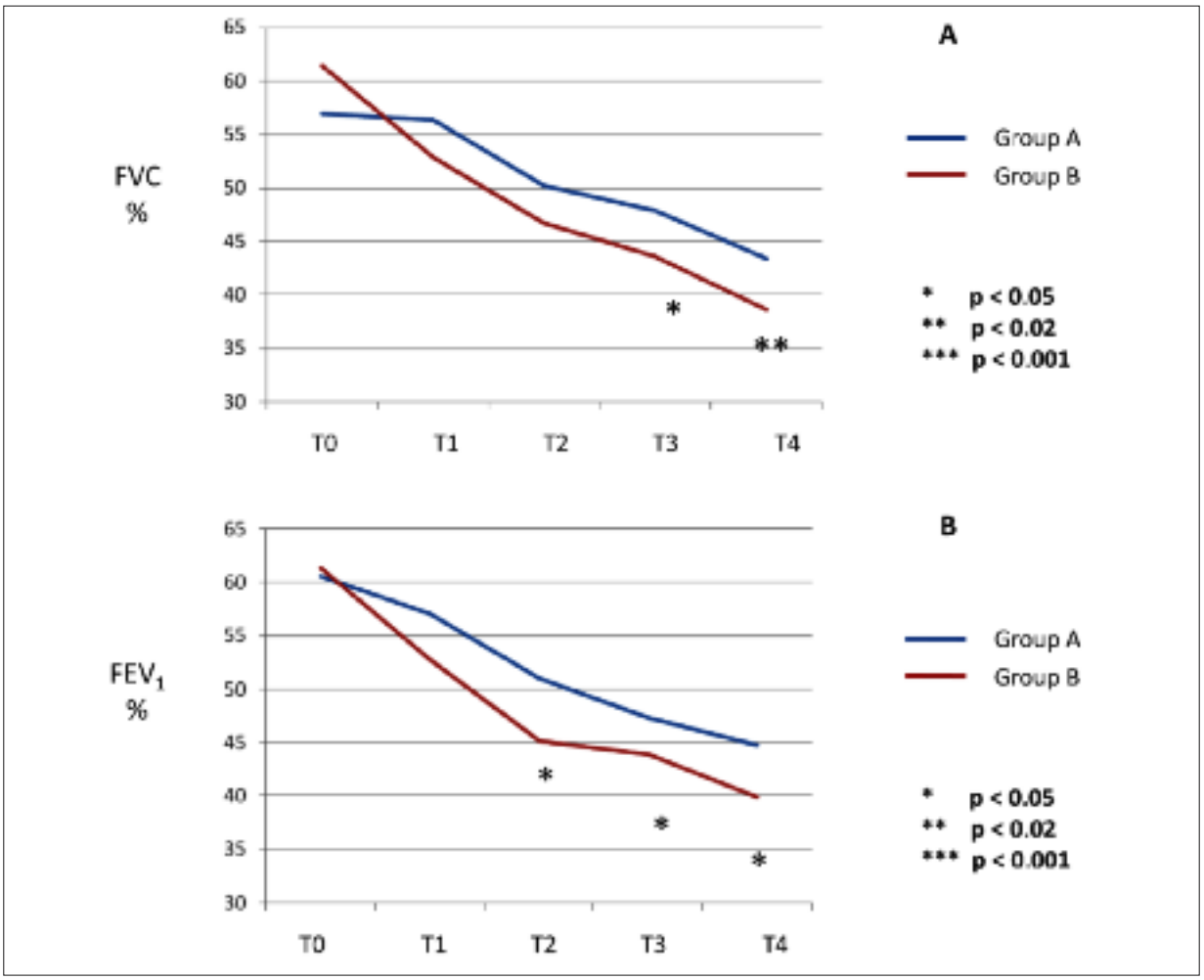

Figure 2. Trend of Forced Vital Capacity (FVC) ***(A)*** and Forced Expiratory Volume in one second (FEV_1) ***(B)*** in both

gressive and fatal. The involvement of the respiratory muscles is a major adverse prognostic factors, whereas more than 60% of cases the symptoms do not manifest until ventilatory failure or the development to hypoxemia and hypercapnia[13]. Tsara et al[14] showed that only 39.3% of the patients reported dyspnea associated with reduction of the MIP and FVC; the remaining percentage only showed an alteration of functional parameters. Several studies[15-18] showed that baseline FVC could be considered a predictor of survival in ALS. This evidence was confirmed by a cohort study[19], developed in 20 years which showed that FVC reduction was a negative prognostic index and highlights that a single measurement of this parameter could serve as a predictor of survival. In our study, all patients presented at Time 0 reduced value of FVC. This value was found to have a decrease trend in both groups we examined. However, we detected as long as statistically significant difference in FVC between Group A and Group B patients. This difference can be explained whereas an adequate maintenance of a ventilatory capacity by the Group A. In a retrospective study on respiratory and ventilatory function in ALS patients, Leonardis et al[20] considered the effectiveness of NIV as an indicator of improving the quality of life and therapy influencing pulmonary function indices. In fact, the patients were divided according to the use of NIV. In the patients with NIV, the rate of FVC reduction was statistically significantly lower than in those without NIV. The decline of PImax and PEmax was not statistically significant. In our study we showed a significant difference regarding the FCV and, in addition, we showed that PImax and PEmax were statistically significant lower in patients in Group B.

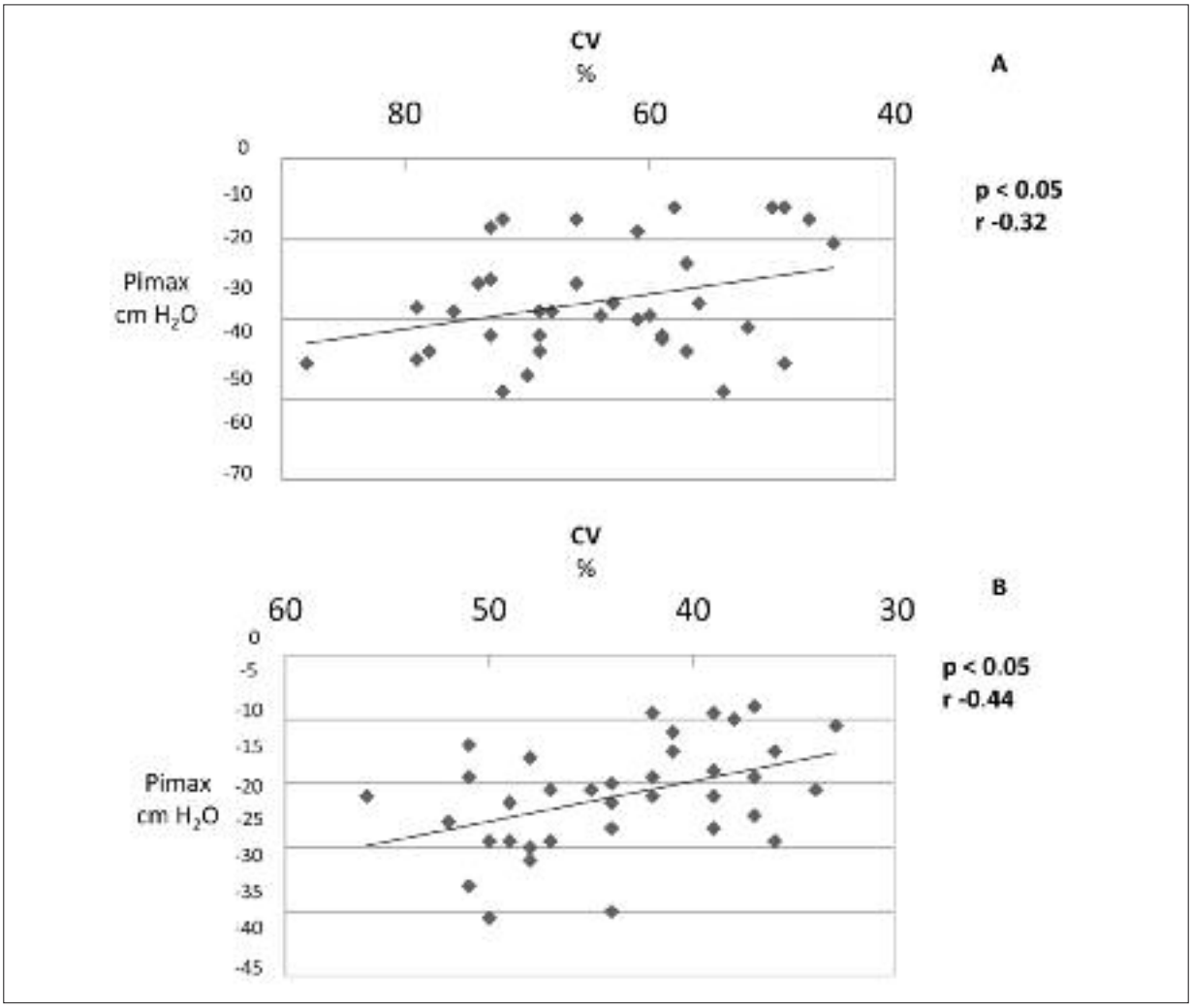

Figure 3. Inverse Correlation between Vital Capacity (CV) and Maximal Inspiratory Pressure (PImax) in all patients at Time 0 ***(A)*** and at Time 4 ***(B)***.

The chest wall and respiratory muscles are the components, along with pleura, of the respiratory pump, and they need to function normally for effective ventilation. Patients with neuromuscular diseases develop significant respiratory muscle weakness. Diseases of these structures result in lung restriction, impaired ventilatory function, and respiratory failure. Neuromuscular disorders, such as ALS, induce a restrictive lung diseases with a low RV, VC and TLC that affect an integral part of the respiratory system, a vital pump. In our report we analyzed TLC and we showed a statistically significant difference between the groups that we considered from Time 0 to Time 3 and Time 4, despite a reduction of this value for all patients because of the underlying disease.

The guidelines of the European Federation of Neurological Societies (EFNS)[5] point out that the blood exchange abnormalities (especially hypercapnia) are found in the late stage of the disease. In fact, hypoxemia and hypercapnia, not always coincide with dyspnea[21,22]. These contrast to Polkey et al[23], which showed that all patients studied were characterized by hypoxemia and hypercapnia, but with severe dyspnea. In our study no patient reported dyspnea during first visit but they had a reduction of lung function indices, not yet associated to an impairment of pulmonary gas exchange. However the arterial blood gas values had a decreasing trend in patients who had initially rejected NIV from the first control. About patients who early started

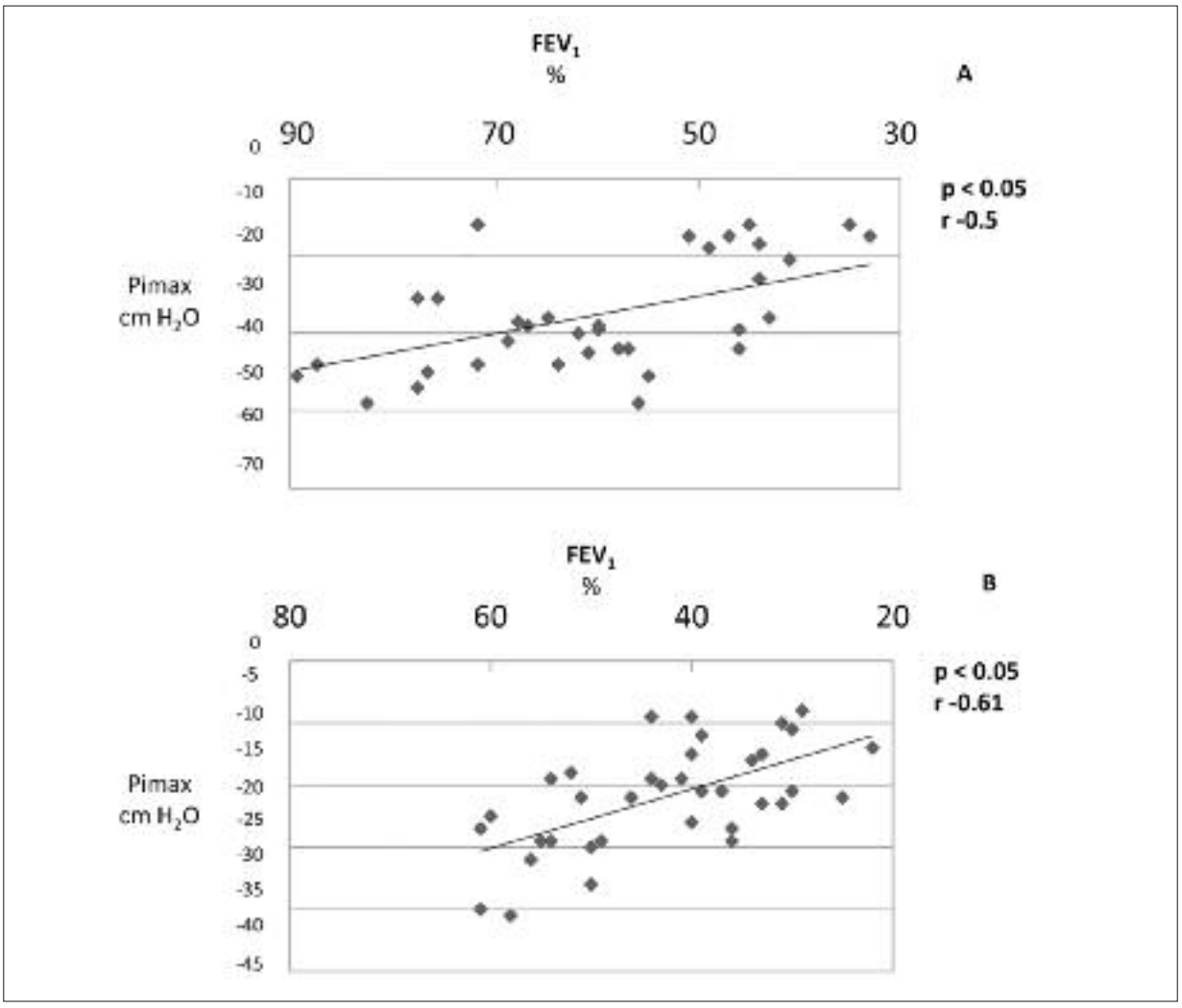

Figure 4. Inverse Correlation between Forced Expiratory Volume in one second (FEV_1) and Maximal Inspiratory Pressure (PImax) in all patients at Time 0 ***(A)*** and at Time 4 ***(B)***.

NIV (Group A), we never found a pH value < 7.35 during follow-up. In contrast the Group B, had significantly lower values of pH and pO_2, as well as values of pCO_2 much higher. Farrero et al[24] evaluated patients with ALS and in therapy with NIV. All patients were divided into two groups based on the time to start the NIV. The results showed that the value of FVC and hypercapnia were worse in patients who started NIV later but there were no differences in the other blood gas parameters between the two groups. Similarly, Almeida et al[25], estimated that hypercapnia should be considered as a significant parameter about the decrease of lung function in patients with ALS. The results also showed correlations between PImax and PEmax confirming the importance in the clinical evaluation of follow-up. Our study showed similar results. However, in addition we emphasized that hypoxia, decreased oxygen saturation, increased lactate and bicarbonate concentration have different values in the two groups with respect to time of start NIV. In fact, lactate improved over time once NIV was started[26]. These findings are confirmed by the improvement of the Group B as a result of use of NIV. Few evidences[27,28] are about the role of peak expiratory flow (PEF) and FEV_1[29,30]. In our work we showed statistically significant differences between Group A and Group B about the PEF and FEV_1. The correlations we have performed highlights the importance of FEV_1 as a negative prognostic index of lung function in pa-

tients with ALS showing that the progressive decrease of this parameter is proportional to the worsening of the PImax. Fregonezi et al[31] showed that the deterioration of the PImax was prior to the decrease in lung function as assessed by the FVC. In our study, we evaluated this aspect stressing that the PImax is correlated also with the vital capacity (VC). This evidence highlights the importance of PImax as a parameter for the deterioration of muscle strength and also the importance of the VC and FEV_1 as predictors factors for the decline of lung function in patients with ALS.

Conclusions

Our study highlights the importance of noninvasive mechanical ventilation as a treatment for patients with ALS and also shows that the early start of NIV is important in order to postpone the function decline and the decrease of respiratory muscle strength.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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