Amyotrophic lateral sclerosis
Prospective study on respiratory parameters

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ABSTRACT
Objective: To verify how efficient respiratory parameters are in the follow-up of subjects with amyotrophic lateral sclerosis (ALS) and to observe possible correlations between respiratory and nutritional functions. **Method:** Sixteen patients with probable or defined ALS were selected and evaluated over eight months using the following respiratory parameters: spirometry, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), arterial gasometry and pulse oximetry; and nutritional parameters such as body mass index (BMI) and percentage weight loss. **Results:** P_aCO_2 was a significant parameter to follow up disease evolution (p=0.051). There was significant correlation between MIP and MEP (r: 0.83); BMI and MIP (r: 0.70); BMI and MEP (r: 0.72); pulse oximetry and forced vital capacity (r: 0.57). **Conclusion:** P_aCO_2 was shown to be an efficient and significant parameter in the measurement of respiratory impairment; the correlations among MIP, MEP and BMI indicated that these are significant parameters for periodic clinical evaluation.
Key words: amyotrophic lateral sclerosis, maximum inspiratory pressure, maximum expiratory pressure, body mass index.

Esclerose lateral amiotrófica: estudo prospectivo de parâmetros respiratórios

RESUMO
Objetivo: Verificar a eficácia dos parâmetros respiratórios na evolução de indivíduos com esclerose lateral amiotrófica (ELA) e identificar possíveis correlações entre função respiratória e nutricional. **Método:** 16 pacientes com diagnóstico provável ou definido de ELA foram selecionados por critérios definidos e avaliados, durante 8 meses, através de parâmetros respiratórios: espirometria, pressão inspiratória máxima (PIM), pressão expiratória máxima (PEM), gasometria arterial e oximetria de pulso; e parâmetros nutricionais: índice de massa corporal (IMC) e porcentagem de perda de peso. **Resultados:** P_aCO_2 foi um parâmetro significativo para acompanhar a evolução da doença (p=0.051). Houve correlação significante entre PIM e PEM (r: 0.83); IMC e PIM (r: 0.70); IMC e PEM (r: 0.72); oximetria de pulso e capacidade vital forçada (r: 0.57). **Conclusão:** P_aCO_2 foi marcador eficaz e significante para medir o comprometimento respiratório; correlações entre PIM, PEM e IMC indicaram ser bons parâmetros nas avaliações clínicas periódicas.
Palavras-chave: esclerose lateral amiotrófica, pressão inspiratória máxima, pressão expiratória máxima, índice de massa corporal.

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Amyotrophic lateral sclerosis (ALS) is a degenerative disease that affects motor neurons in the brain and spinal cord. Clinical characteristics include limb weakness, difficulties in swallowing, speaking and breathing[1].

Bulbar dysfunction, resulting from lesions in either the corticobulbar tract or

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motor nuclei, increases the risk of aspiration pneumonia, aggravating the respiratory function, which is sometimes already impaired. Swallowing dysfunction leads to nutritional deficiency and consequently to a morbid spiral that increases respiratory muscle fatigue[2]. Nutritional status is aggravated unless it is routinely monitored in order to identify when a patient shows weight loss and malnutrition[3]. Early intervention helps to delay morbidity.

This study was aimed at evaluating how efficient respiratory parameters are in the assessment of ALS evolution, as well as observing possible correlations between respiratory and nutritional functions.

METHOD

Patients with defined or probable ALS, according to the revised El Escorial, 1998[4], were followed up at the outpatient clinic for Neuromuscular Diseases of the University of Campinas (UNICAMP), and participated in a cross-sectional study with respiratory and nutritional evaluation (first evaluation) and a longitudinal prospective study for eight months, during which respiratory parameters were observed. All the patients were in use of Riluzole and were sporadic cases. Those patients requiring assisted mechanical ventilation or with a nasogastric tube or gastrotomy at the beginning of the study were excluded.

The ethics committee of the School of Medical Sciences - UNICAMP approved the study and all patients signed an informed consent form (protocol 347/2006).

In the initial evaluation, named the first evaluation, patients were assessed using spirometry; maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), gasometry and pulse oximetry. Three subsequent evaluations every two months included the same tests, except for spirometry.

Spirometry was carried out in the seated position, and included measurement of forced vital capacity (FVC) and peak expiratory flow (PEF) expressed as percentages of the predicted value, according to sex and age.

Maximum inspiratory pressure and maximum expiratory pressure: MIP and MEP measurements were carried out, in accordance with Black and Hyatt, and based on the residual volume and total pulmonary capacity, respectively, at three consecutive moments, with a 30-second interval between maneuvers. The highest value was considered.

Arterial gasometry: partial arterial oxygen pressure (P_aO_2) <83 mmHg and partial arterial carbonic gas pressure (P_aCO_2) >45 mmHg were considered abnormal[6].

Pulse oximetry was measured using a Moryia 1001 model oximeter.

Symptoms of respiratory muscle weakness: dyspnoea on exertion, morning headaches, fatigue, disturbed sleep (insomnia, excessive daytime somnolence, nocturia, impatience)[7].

Body mass index (BMI): BMI=body mass kg/height m²; a value between 18.5 and 24.9 kg/m² was considered normal[8].

Percentage weight loss (WL%) was determined by comparing usual and current patient weight. Weight loss of 10% indicated malnutrition and above 10% indicated severe malnutrition[9].

Body mass index and percentage of weight loss were measured in the first evaluation.

Statistical analysis

In order to compare the evolution of continuous variables, the analysis of variance (ANOVA) was used for repeated measurements with Rank transformation. Correlations between variables were found using Spearman's coefficient. Values were classified as: 0 to 0.19 – weak correlation; 0.2 to 0.39 – mild correlation; 0.4 to 0.59 – moderate correlation; 0.6 to 0.79 – important correlation; 0.8 to 1 – almost perfect correlation[10]. The Statistical Analysis System (version 9.1.3) and Microcal Origin software (version 5.0) were used. A significance level was p≤0.05.

RESULTS

Table 1 shows the demographic data of the patients; four cases (2, 5, 6 and 9) had predominant bulbar ALS and 12 had predominant appendicular ALS. Thirteen male patients and three females were within normal range of pulmonary function test parameters, pulse oximetry and arterial gasometry. The MIP reached 49% of what was expected, according to the patients' sex and age and the MEP was 34.7%, indicating restrictive muscle impairment.

The mean BMI for patients subjected to the test (n=10) was 22.54, which is within normal range, although WL% indicated that three patients were nutritionally at-risk, five had severe malnutrition and two had gained body mass (patients 1 and 8, Table 1). The mean WL% was 13.3%.

Five out of 16 patients evaluated for P_aCO_2 succeeded in carrying out the tests on a continuous basis in the first, second and fourth evaluations. In these patients, the mean values of P_aCO_2 ranged between 34.74 in the first evaluation and 39.12 mmHg in the last one, with statistical relevance (p=0.0513) (Figure). The mean P_aO_2 of these patients ranged between 87.16 in the first evaluation and 89.18 mmHg in the last one, with no statistical relevance (p=0.7504).

Maximum inspiratory pressure was evaluated four times in 15/16 patients and MEP in 14/16. The MIP mean ranged between –65.67 cmH₂O (first exam) and –64.33 cmH₂O (fourth exam); this decrease was not significant (p=0.7764). The MEP mean ranged between 74.29 cmH₂O and 71.79 cmH₂O, also with no significance (p=0.7671). The MIP and MEP values showed high variability and great standard deviation.

The mean values of pulse oximetry showed slight vari-

Table 1. Descriptive variables in the first evaluation.

Cases	Age	Sex	MIP	MEP	Oxi%	Spirometry		Gasometry		BMI	%WL
						FVC%	PEF%	PaO2	PaCO2		
1	59	M	−55	50	97	98	114	93.1	34.6	25.1	−15.4
2	40	F	−10	nap	95	nap	nap	91.2	37.2	18.2	14.3
3	49	M	−45	40	94	60	59	102	38.4	18.1	26.4
4	46	M	−135	130	96	109	103	61	29.1	24.2	14.6
5	32	F	−10	10	86	54	47	134	29	19.5	7.4
6	42	M	−45	30	97	nap	nap	79	37	19.9	21.8
7	53	M	−110	95	98	87	78	85.7	30.2	27	2.1
8	44	M	−100	80	99	96	104	89.6	35.8	24.4	−1.2
9	37	M	−35	45	97	nap	nap	92	38	21.3	8.7
10	36	M	−60	80	94	80	95	73	36	27.7	11.1
11	52	M	np	np	96	np	np	70.7	38.6	–	–
12	62	F	−70	60	92	80	92	75.1	33.6	–	–
13	41	M	−30	60	96	52	49	75	42	–	–
14	49	M	−110	125	96	91	86	86.9	39.5	–	–
15	43	M	−45	85	96	102	102	109	33	–	–
16	35	M	−125	150	95	76	73	np	np	–	–
Mean	45	–	65.66	74.28	95.25	82.08	83.5	87.82	35.46		
SD	8.4	–	40.78	40.32	2.97	18.82	22.45	17.89	3.87		
Median	44.5	–	55	70	96	52	47	86.9	36		
Min	32	–	10	10	86	83.5	89	61	29		
Max	62	–	135	150	99	109	114	134	42		

M: male; F: female; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; Oxi: Pulse oximetry; FVC%: percentage of forced vital capacity; PEF%: peak expiratory flow percentage; P_aO_2: partial arterial oxygen pressure; P_aCO_2: partial arterial carbonic gas pressure; BMI: body mass index; %WL: percentage weight loss; nap: not able to perform the test; np: test not performed.
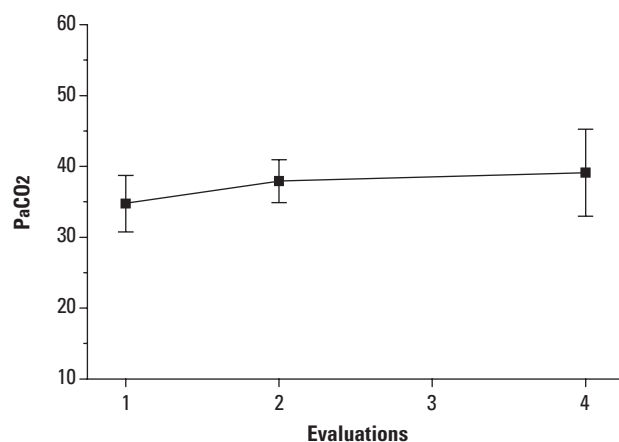
Figure. Mean and standard deviation of P_aCO_2 evolution in the three evaluations. ANOVA Test, p-value=0.0513.

Table 2. Spearman's correlation coefficient between respiratory and nutritional parameters

	BMI	%WL	MIP	MEP
P_aO_2	−0.527	−0.224	−0.50222	−0.44904
P_aO_2	0.117	0.53	0.0672	0.1237
n	10	10	14	13
P_aCO_2	−0.418	−0.491	−0.26549	−0.15152
P_aCO_2	0.229	0.15	0.3589	0.6212
n	10	10	14	13
Oxi	0.443	−0.474	0.23863	0.13887
Oxi	0.2	0.166	0.3917	0.6359
n	10	10	15	14
MIP	**0.70123**	−0.17683	–	**0.83500**
MIP	**0.0239**	0.6250	–	**0.0002**
n	10	10	–	14
MEP	**0.72804**	−0.23431	–	–
MEP	**0.0262**	0.5440	–	–
n	9	9	–	–

P_aO_2: partial arterial oxygen pressure; P_aCO_2: partial arterial carbonic gas pressure; Oxi: pulse oximetry; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; BMI: body mass index; %WL: percentage weight loss; n: number of patient.

ation in the 16 patients: 95.25% in the first evaluation and 95.13% in the last one, with no significant statistical variance (p=0.1816).

Strong correlation between MIP and MEP was observed (r: 0.83500; p=0.0002). Body mass index strongly

Table 3. Spearman's correlation coefficient between spirometry and other variables.

	FVC%	PEF%
MIP	0.49209	0.37544
MIP	0.1041	0.2291
n	12	12
MEP	0.46046	0.24562
MEP	0.1320	0.4416
n	12	12
Oxi	**0.57688**	0.54199
Oxi	**0.0496**	0.0687
n	12	12
P_aO_2	−0.05467	−0.15455
P_aO_2	0.8732	0.6500
n	11	11
P_aCO_2	−0.34169	−0.10909
P_aCO_2	0.3037	0.7495
n	11	11
BMI	0.28571	0.42857
BMI	0.5345	0.3374
n	7	7
%WL	−0.32143	−0.57143
%WL	0.4821	0.1802
n	7	7

MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; Oxi: pulse oximetry; P_aO_2: partial arterial oxygen pressure; P_aCO_2: partial arterial carbonic gas pressure; BMI: body mass index; %WL: percentage weight loss; FVC%: percentage of forced vital capacity; PEF%: peak expiratory flow percentage; n: number of patient.

correlated with MIP (r: 0.7012; p=0.0239) and with MEP (r: 0.7280; p=0.0262), with no significance in other comparisons (Table 2).

There was moderate significance in correlation between pulse oximetry and FVC values (r: 0.5768; p=0.0496), with no significance in other comparisons (Table 3).

DISCUSSION

P_aCO_2 proved to be an efficient indicator in the evaluation of respiratory impairment throughout the eight months. There was an increase in the mean values, even though they remained within the normal range, that is, lower than 45 mmHg. Lyall et al.[11] reported that P_aCO_2 is one of the main parameters used as an indication for starting noninvasive mechanical ventilation in ALS, although it is not very sensitive due to the late manifestation of hypercapnia. It can be supposed that as the disease evolves, hypercapnia may trigger a vicious cycle of pulmonary function worsening and the necessity of ventilation support.

Lyall et al.[11] recruited 81 patients with ALS to evalu-

ate their hypercapnia as a respiratory function complication prognosticator. The P_aCO_2 mean was 41.7 mmHg and only 18% of the subjects had hypercapnia. The authors reported that in the presence of a mild weakness, P_aCO_2 drops below normal levels and hyperventilation occurs to compensate for alveolar hypoxemia.

According to the American Academy of Neurology there is a lack of evidence of the best parameter to detect respiratory failure. There are no previous studies that evaluate the relationship between respiratory muscle strength and ventilation failure in large samples of ALS patients[12].

In this study, arterial gasometry and pulse oximetry values remained normal during the eight-month follow-up. The MIP and MEP values were 60% below what was expected after the first evaluation, which already indicates the beginning of respiratory muscle impairment [5] even though the data was not statistically significant.

It is a common belief that P_aCO_2, together with pulmonary hypoventilation signs, may indicate a respiratory impairment throughout time, and that it is an indicator for preventive procedures such as, for instance, the use of noninvasive ventilation support[7].

Vital capacity is one of the most used clinical tests to monitor pulmonary function[13]. Patients with severe restrictive ventilation impairment resulting from neuromuscular diseases show a more significant reduction of pulmonary volume than maximum pressures. Therefore, vital capacity is a more sensitive measurement in the evaluation of respiratory muscle strength in the advanced stage of these diseases[14].

Jackson et al.[15], in their studies on pulmonary function in ALS, reported that most of the patients, even though their FVC was 70% above expected, had MIP lower than 60 cm H_2O, which may reflect an early respiratory insufficiency. Our study corroborates that, since the FVC mean was 82% of the expected value and the MIP mean was 49% of what was expected.

Pulse oximetry was carried out during outpatient clinical evaluations, and it was not possible to monitor our patients during nights. Even so, there was a positive correlation between oximetry and FVC, demonstrating the importance of evaluating respiratory parameters on a regular basis.

Dysfunction of inspiratory, expiratory and bulbar muscles may result in oxygen desaturation due to hypercapnia, coughing dysfunction and excessive aspiration of saliva. In those conditions, noninvasive ventilation support helps to normalize P_aCO_2 values and oxygen desaturation[16].

There was no correlation between pulse oximetry and arterial gasometry, probably because patients had not yet shown severe respiratory impairment, with hypercapnia and symptoms of respiratory muscle weakness such as dyspnea on effort, fatigue, morning headache or sleep dis-

orders. Constant measurement of oxygen saturation is assumed to be necessary to decide what is the ideal moment to start noninvasive mechanical ventilation when a patient complains of what is evidence of nocturnal pulmonary hypoventilation.

Lyall et al.[11] demonstrated significant correlation between P_aCO_2 and MIP and MEP. The low values obtained in respiratory muscle strength tests led to hypercapnia. Hypercapnia occurs when weakness becomes severe, leading to ventilation failure. As no correlation between these parameters was found, it is assumed that weakness of respiratory muscles in our patients was mild to moderate.

Just like Lechtzin[17], we assume it is a wise procedure to measure P_aCO_2 when spirometry is unable to explain symptoms of respiratory complications in patients or if they report sleeping difficulties.

The most significant correlation of BMI and respiratory parameters was between MIP and MEP, in which patients with greater weakness and reduced body mass showed reduced respiratory muscular strength. There was no correlation between BMI and spirometry since the patients presented with normal values for FVC and spirometry. This is probably because spirometry is not sensitive enough to evaluate ventilation function in initial or moderate stages of respiratory discomfort, as reported by Schoesmith et al.[18].

The results found in this study corroborate those obtained by Silva et al.[19] who also found correlation between BMI and FVC and between BMI and MEP in patients who presented with bulbar ALS. The correlation was strong, even considering MIP and MEP indicators are not a sensitive measure in the evaluation of the respiratory function in these patients, due to oro-pharyngeal weakness, as described by Fitting et al.[20].

Desport et al.[21] evaluated nutritional status through the use of BMI in ALS patients. In their study, the survival rate time was shorter in malnourished patients when compared to the group considered as normal. The nutritional status was a decisive factor for survival, as a vital capacity 60% higher than the expected value. However, both measurements were considered as independent prognostic values.

In the patients that had BMI assessed, the FVC mean was 83.4% of the predicted value. Only two out of the 10 patients who had their BMI evaluated in the first visit had values below normal. When evaluated by WL%, five patients showed severe malnutrition, in other words, a loss greater than 10%, according to Mahan and Stump[9] values. Rio and Cawadias[3] suggest that body weight to evaluate nutritional status in ALS patients should not be underestimated; however, impaired mobility may be a limitation in the measurement of this parameter. Nutritional support may delay weight loss and muscular atrophy. Studies have demonstrated that body weight loss associated with bulbar changes (dysphagia and breathing) requires early and specific nutritional support[22].

The intervention of the multidisciplinary team, such as physicians, physiotherapists, nutritionists and speech therapists, is necessary to evaluate the patient as a whole. A more comprehensive healthcare protocol allows the patient an improved quality of life.

In conclusion, P_aCO_2 was shown to be an efficient and significant parameter to in the measurement of respiratory impairment. The correlations among MIP, MEP and BMI indicated that these are significant parameters for periodic clinical evaluation.

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