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Breathing pattern and respiratory mechanics in patients with amyotrophic lateral sclerosis

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ABSTRACT: The aim of this study was to evaluate the time course of breathing pattern and respiratory mechanics in patients with amyotrophic lateral sclerosis (ALS).

A study was conducted on 25 out of 38 eligible ALS patients. Neurological status, arterial blood gases (ABGs), spirometry, breathing pattern (minute ventilation (V'_E), tidal volume (V_T), respiratory frequency (f_R), duty cycle (duration of inspiration/duration of total breathing cycle (t_I/t_{tot})), respiratory drive ($P_{0.1}$)), respiratory mechanics (oesophageal pressure (P_{pl}), dynamic compliance ($C_{L,dyn}$), pressure time product (PTP) and index (PTI), work of breathing (WOB)), and respiratory muscle (RM) strength as assessed by maximal oesophageal pressure ($P_{pl,max}$) were evaluated at presentation (t_0) in all patients and after 6 months (t_6) in 11 patients.

At t_0, the mean values of the degree of neurological impairment were 60±20 and 103±30 as assessed by the Norris scale and Medical Research Council (MRC) score, respectively. From the time of the first neurological symptom, survival time ranged 7–50 months. Diurnal ABGs were normal. A mild restrictive pattern was observed, a forced vital capacity (FVC) <70% of predicted being present in 45% of patients, only FVC % pred (r=0.59; p<0.05), forced expiratory volume in one second (FEV_1) % pred (r=0.53; p<0.05) and survival (r=0.64; p<0.05) showing a significant correlation with the Norris scale. A $P_{pl,max}$ <30 cmH_2O was associated with a significantly greater mortality, $P_{pl,max}$ being correlated with survival (r=0.79, p<0.05). At t_6, f_R, f_R/V_T, $P_{0.1}/P_{pl,max}$, were significantly increased in comparison to t_0, while FVC % pred, vital capacity (VC) % pred, FEV_1 % pred, V_T and $P_{pl,max}$ were significantly reduced.

These results suggest a progressive deterioration in breathing pattern and in respiratory muscle strength with progression of disease.

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Amyotrophic lateral sclerosis (ALS) is a progressive, degenerative and fatal disease affecting both upper and lower motor neurons. The involvement of the respiratory muscles (RMs) leading to dyspnoea and respiratory failure, is the most common cause of death in these patients [1, 2]. Respiratory symptoms usually appear late, and the monitoring of lung and RM function have been reported to be the best prognostic indicators in these patients [3–5]. Most patients with ALS have reduced forced vital capacity (FVC) which is reported to be related to the presence of respiratory symptoms, and declines progressively with time [3, 4, 6]. RM impairment has been showed to be related to the stage of disease at presentation and to decline linearly with a great deal of interpatient variability [4].

Although other investigators have studied pulmonary mechanics in patients with neuromuscular diseases [7], to our knowledge there is little information on breathing pattern and respiratory mechanics [8], and on their time course in the natural history of the disease.

The objectives of this study were to describe the time course of breathing pattern and chest wall mechanical indices in patients with ALS and to determine the relationships, if any, between these indices and the progression of disease as assessed by common clinical scoring.

Methods

Patients

From October 1992 to February 1995, 38 consecutive patients examined at the neurology laboratory, with a diagnosis of ALS, either spinal or bulbar [9], were considered for the study. All patients underwent a complete standard laboratory radiograph, electromyography (EMG), multimodal evoked potentials and magnetic resonance imaging (MRI) of the brain and cervical spinal cord to exclude other diseases mimicking ALS. Diagnosis of definite ALS was made when the following criteria were met [10]: 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. Moreover, diagnosis of idiopathic ALS was

accepted if exposure to infections and toxins or the presence of neoplasm, metabolic disorders or other progressive diseases were ruled out. No patient suffered from familial ALS. Exclusion criteria were: 1) presence of an episode of acute respiratory failure (ARF) at the time of presentation requiring mechanical ventilation (MV); 2) presence of a tracheotomy; and 3) inability to perform respiratory measurements.

Most patients were receiving conventional symptomatic therapy (nonsteroid anti-inflammatory drugs, amitriptyline). None of the patients underwent steroid or immunosuppressive treatment, or received other drugs known to affect RM function [11]. Informed consent was obtained verbally. The study was approved by the Ethics Committee of the Salvatore Maugeri Foundation IRCCS.

Measurements

At baseline ($t0$) and at 6 months ($t6$), patients were submitted to the following monitoring.

Anthropometric data. Age, sex, height and weight were recorded. Percentage of ideal body weight (%IBW) was computed referring to the Metropolitan Life Insurance Company Table [12]. Body mass index (BMI) was calculated as body weight/height^2.

Neurological status. Clinical neurological examination with serial motor function and disability evaluation was performed by the same two neurologists (DF and M. Poloni) with specific experience both of application of the scales and of clinical trials on ALS.

Rating scales. Fifteen muscles were examined manually and graded according to the British Medical Research Council (MRC) score. This score assesses the segmental force for upper and lower limbs, and decreases with worsening of force, the maximum value being 150: 80 for upper limbs and 70 for lower limbs [13]. Functional quantitative evaluation was performed by means of the Norris ALS scale. This disability score was developed specifically for ALS, and includes evaluation of the function of upper and lower limbs, also taking into account bulbar function. This score uses 34 items rated with a value from 0 to 3; and the normal score is 100 [14].

Survival. Survival time was considered as the total number of months from the first symptom to death.

Lung function tests. Dynamic lung volumes and flow-volume loops were assessed by means of a portable spirometer (Pony class 1 Type B; COSMED, Rome, Italy); both digital readout and paper tracings were obtained. The highest values of vital capacity (VC), FVC and forced expiratory volume in one second (FEV1) observed in three tests were considered and expressed as percentage of the predicted values (% pred), according to European Respiratory Society (ERS) standards [15].

Daytime and night-time blood gases. Arterial blood gases (ABGs) were assessed by means of an analyser (EGA system; Ciba Corning, Rome, Italy), using blood samples drawn from the radial artery while the patients were breathing room air. Arterial Oxygen saturation (S_{a,O_2}) was continuously monitored during the night in 19 out of 25 patients by means of a portable pulsed oximeter with an extensive solid-state memory (Pulsox 5; Minolta Camera, Osaka, Japan). The pertinent definition of desaturation was: percentage of recorded time spent with S_{a,O_2} <90%.

Breathing pattern and mechanics. In the patients and in 10 healthy control subjects, all data were recorded in the same session in a semi-recumbent position, shortly after admission. Flow was measured by means of a flow sensor (Var Flex Flow transducer; CP-100 Bicore, Irvine, CA, USA) connected to a mouthpiece. Airway pressure was measured through a catheter attached to the flow sensor. Pleural pressure (P_{pl}), estimated by measuring oesophageal pressure swings, were measured by means of an oesophageal catheter with a 10 cm balloon at the distal end (part No. 700-3-100; Bicore, Irvine, CA, USA) passed transnasally and positioned in the lower third of the oesophagus. The position of the catheter was checked by means of the occlusion technique [16]. The oesophageal balloon and the flow sensor were connected to a portable monitor (CP-100 Bicore) providing real time display of flow, volume, and P_{pl} tracings. After 15 min of breathing with the oesophageal catheter and having reached a good level of confidence with the set, airway pressure, airway flow and P_{pl} were transmitted to the monitor and recorded for 180 s after the patients had developed at least a 2 min "steady state" period in their breathing pattern. The final data were collected as the average of at least three breaths, eliminating those affected by artifactual P_{pl} variations. Minute ventilation (V'_E) and breathing pattern (tidal volume (V_T), respiratory frequency (f_R), f_R/V_T ratio, respiratory timing and duty cycle (duration of inspiration/duration of total breathing cycle (t_I/t_{tot})), mean inspiratory flow (V_T/t_I)) were assessed by the flow signal. P_{pl} swings were analysed, measuring peak amplitude from the immediately preceding end expiratory value. Patient work of breathing (WOB) was assessed by calculating the area under the P_{pl} *versus* lung volume curve during the negative deflection of P_{pl} tracings [17]. Respiratory drive ($P_{0.1}$) was calculated as the change in P_{pl} occurring between the time 100 ms prior to the start of airflow, and the onset of flow. From $P_{0.1}$ and V_T/t_I, respiratory impedance ($P_{0.1}/V_T/t_I$) was calculated. Maximal static inspiratory P_{pl} ($P_{pl,max}$) was assessed by means of a Muller manoeuvre during a maximal inspiratory effort generated after manual occlusion of the flow transducer starting from functional residual capacity (FRC). The subjects were verbally encouraged to achieve maximal strength. The highest value (most negative P_{pl}) of three tests was considered in data analysis [18]. Pressure time index (PTI) was calculated as $P_{pl}/P_{pl,max} \times t_I/t_{tot}$. Dynamic compliance ($C_{L,dyn}$) and pressure time product (PTP), were also calculated from P_{pl}, flow and volume data. Reliability and accuracy of the Bicore CP-100 pulmonary device in spontaneously breathing patients has been demonstrated previously [19].

Statistical analysis

All the data (parametric and nonparametric) are expressed as mean±SD. The normal distribution of all

Table 1. – Demographic, anthropometric and neurological data of patients at presentation (*t*0)

Patients n	25
Gender males/females	12/13
Age on admission yrs	65±10
Weight kg	63±16
Ideal body weight %	94±5
Height cm	168±9
BMI (males) $kg \cdot m^{-2}$	20±5
BMI (females) $kg \cdot m^{-2}$	16±6
Age at diagnosis yrs	63±10
Duration of disease months	25±29 (range 6–37)
MRC score	103±30
Norris scale	60±20

Values are presented as absolute number or mean±SD. BMI: body mass index; MRC: Medical Research Council.

baseline variables recorded was evaluated with Kurtosis, Skeweenes and Shapiro-Wilk's W Test. A two-sample t-test or the Mann-Whitney rank sum test was used for the nonparametric variables between: 1) patients dead and alive for all the baseline variables; and 2) the two different subgroups according to Norris severity. Spearman rank correlation was used to test and to indicate the relationships between the duration of disease, and functional and neurological variables. The survival analysis was estimated with the Peto-Prentice (General Wilcoxon) test. In order to use the parametric discriminant analysis and correlation tests, variables found to be nonparametric were transformed as proposed by ARMITAGE and BERRY [20]. Logistic stepwise regression analysis was performed among all previously described anthropometric, spirometric, blood gas, breathing pattern and mechanical variables, to confirm the data obtained with stepwise discriminant analysis. A p-value of less than 0.05 was considered significant. All the results of multiple comparison were corrected using the Bonferroni test.

Results

Thirty eight consecutive patients with ALS were considered for the study. Five out of 38 patients were excluded due to an ARF episode requiring MV at the time of presentation, two patients refused, four were unable to perform evaluation, and two had a tracheotomy. Twenty five patients satisfied the acceptance criteria: five (20%) had bulbar involvement and 20 (80%) spinal prevalence. Demographic, anthropometric and neurological status as assessed by MRC and Norris scores, and duration of disease at *t*0 for patients in the study are shown in table 1. At *t*0, nutritional status as assessed by IBW was in the normal range (table 1) and did not show any significant change at *t*6.

At *t*6 10 out of 25 patients (40%) had died (two out of five (40%) with bulbar involvement and eight out of 20 (40%) with spinal involvement), and four out of 15 survivors were unable to attend the session. Differences at presentation among patients according to the Norris scale and according to whether patients had died or survived are shown in tables 2, 3, 4 and 5. Patients presenting with more severe neurological impairment according to the Norris scale were not different for spirometric and blood gas values, but showed lower V_T/t_I, V_T, $P_{pl,max}$ and higher f_R/V_T, $P_{0.1}/P_{pl,max}$ and PTI.

Table 2. – MRC scores and respiratory function at presentation according to the severity of neurological status

	Norris scale		p-value
	<60 (n=16)	>60 (n=9)	
MRC score	93±24	123±131	<0.01
VC % pred	62±20	78±18	NS
FEV_1 % pred	66±30	71±31	NS
FVC % pred	64±24	85±24	NS
FEV_1/VC %	80±18	77±17	NS
P_{a,CO_2} kPa	5.71±0.66	5.18±0.66	NS
P_{a,O_2} kPa	10.10±1.46	11.43±1.19	NS

Values are presented as mean±SD. MRC: Medical Research Council; VC: vital capacity; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; P_{a,CO_2}: arterial carbon dioxide tension; P_{a,O_2}: arterial oxygen tension; % pred: percentage of predicted value; NS: nonsignificant.

Table 3. – MRC scores and respiratory function at presentation according to outcome

	Outcome		p-value
	Died (n=10)	Survived (n=15)	
Age yrs	70±9	59±8	<0.01
Norris score	54±19	66±20	NS
MRC score	97±35	109±29	NS
Duration of disease months	23±13	27±35	NS
VC % pred	35±10	81±27	<0.001
FEV_1 % pred	46±32	77±25	<0.001
FVC % pred	51±33	80±20	<0.001
FEV_1/VC %	72±21	81±16	NS
P_{a,CO_2} kPa	5.8±0.8	5.3±0.5	NS
P_{a,O_2} kPa	9.7±1.7	11.0±1.4	NS

Values are presented as mean±SD. For definitions, see legend to table 2.

Table 4. – Breathing pattern and mechanics at presentation according to the severity of neurological status

	Controls (n=10)	Norris score <60 (n=16)	Norris score >60 (n=9)	p-value
f_R breaths·min^{-1}	14±6	23±7	21±8	NS
V_T/t_I mL·s^{-1}	452±130	339±110	438±195	<0.03
t_I/t_{tot}	0.41±0.06	0.40±0.05	0.40±0.08	NS
V'_E L·min^{-1}	8.1±2.2	6.8±2.5	8.7±4.0	NS
V_T mL	722±147	353±169	500±216	<0.03
f_R/V_T	29±27	99±65	43±23	<0.03
P_{pl} cmH_2O	7±2.2	7.2±3.1	7.5±3.0	NS
$C_{L,dyn}$ mL·cmH_2O^{-1}	154±55	80±53	117±71	NS
$P_{0.1}$ cmH_2O	1.2±0.4	2±1.2	1.5±1.0	NS
$P_{pl,max}$ cmH_2O	90±20	25±12	50±25	<0.02
$P_{0.1}/P_{pl,max}$	0.01±0.02	0.08±0.02	0.03±0.01	<0.03
PTP $cmH_2O \cdot s \cdot min^{-1}$	172±63	139±50	144±42	NS
PTI	0.05±0.03	0.17±0.06	0.05±0.03	<0.02
WOB J·L^{-1}	0.70±0.22	0.65±0.10	0.64±0.11	NS

Values are presented as mean±SD. f_R: respiratory frequency; V_T: tidal volume; t_I: duration of inspiration; t_{tot}: duration of total breathing cycle; V'_E: minute ventilation; P_{pl}: oesophageal pressure; $C_{L,dyn}$: dynamic compliance; $P_{0.1}$: respiratory drive; $P_{pl,max}$: maximal oesophageal pressure; PTP: pressure time product; PTI: pressure time index; WOB: work of breathing; NS: nonsignificant. p-values are for comparison of those with Norris score <60 and >60.

Table 5. – Breathing pattern and mechanics at presentation according to the severity of neurological status

	Outcome		p-value
	Died (n=10)	Survived (n=15)	
f_R breaths·min^{-1}	28±8	20±6	NS
V_T/t_I mL·s^{-1}	350±100	400±150	NS
t_I/t_{tot}	0.44±0.04	0.39±0.07	NS
V'_E L·min^{-1}	7±2	8±3	NS
V_T mL	305±75	440±213	<0.03
f_R/V_T	111±48	60±55	<0.05
P_{pl} cmH_2O	7.8±4	7.1±3	NS
$C_{L,dyn}$ mL·cmH_2O^{-1}	58±24	116±68	<0.05
$P_{0.1}$ cmH_2O	1.8±1.0	1.7±1.2	NS
$P_{pl,max}$ cmH_2O	21±9	42±23	<0.02
$P_{0.1}/P_{pl,max}$	0.07±0.02	0.04±0.01	NS
PTP cmH_2O·s·min^{-1}	147±59	139±46	NS
PTI	0.22±0.19	0.06±0.03	<0.02
WOB J·L^{-1}	0.79±0.11	0.62±0.10	NS

Values are presented as mean±SD. For definitions, see legend to table 4.

At presentation, mean age (table 3), f_R/V_T, and PTI (table 5) were higher for patients who had died during the follow-up in comparison to survivors, while VC % pred, FEV1 % pred, FVC % pred (table 3), V_T, $C_{L,dyn}$, and $P_{pl,max}$ were more severely compromised (table 5).

The causes of deaths were: acute respiratory failure due to pneumonia (30%); aspiration (10%); severe arrhythmia (20%); acute myocardial infarction (10%); and acute respiratory failure not associated with infectious aetiology (30%). The mean time of survival was 38±37 months (range 7–50); mortality rate during the observation time (October 1992 to February 1995) was 76% (19 out of 25).

Spirometry

Baseline lung function data are shown in table 2. Patients showed a mild restrictive pattern as assessed by a VC<70 % pred in 10 out of 25 (40%) patients. Thirty one per cent of patients showed a flow-volume loop consistent with upper airway dysfunction according to GARCIA-PACHON *et al*. [21]. No significant difference was found in dynamic volumes and ABG between patients with different severity of neurological impairment as assessed by the Norris score (table 2). Only FVC % pred (r=0.59; p<0.05) and FEV1 % pred (r=0.53; p<0.05) showed significant correlation with the Norris scale. Tables 4 and 5 show the time course of dynamic volumes in the individual 11 patients assessed also at t_6. At this time, VC was reduced in all patients, the mean values being reduced to almost half.

Breathing pattern and respiratory mechanics

Tables 6 and 7 present the means and the individual values at t_0 and t_6 of the 11 patients who were able to attend at t_6. In comparison to our laboratory normal data (tables 4 and 5), patients showed a significantly lower $P_{pl,max}$ and V_T, while $P_{0.1}/P_{pl,max}$, f_R/V_T, $P_{0.1}/V_T/t_I$ and PTI were significantly greater. Patients with a more severe level of neurological involvement (as assessed by a Norris score <60) showed lower V_T, V_T/t_I and $P_{pl,max}$, and greater f_R/V_T ratio and PTI in comparison with patients with a Norris score >60 (table 4). No significant relationship was found between the measured parameters and length of disease. In comparison to t_0, the 11 patients able to perform respiratory measurements at t_6 showed f_R, f_R/V_T, $P_{0.1}/P_{pl,max}$, significantly increased (table 7), while FVC % pred, VC % pred, FEV1 % pred (table 6), V_T and $P_{pl,max}$ (table 7) were significantly reduced.

Arterial blood gases

As shown in tables 2 and 3, at t_0 mean values of ABG were in the normal range. Only one patient showed a P_{a,O_2} <8 kPa; eight (32%) showed a P_{a,O_2} <9 kPa. Only three (12%) out of 25 patients showed a P_{a,CO_2} >6 kPa. At t_6, mean values of ABG were still in the normal range: six (54%) patients showing a P_{a,CO_2} ≥6 kPa and three (27%) patients showing a P_{a,O_2} ≤8 kPa (table 6). All 19 patients in whom it was possible to perform non-invasive monitoring of ABG showed periods of desaturation. The average time of recording spent with S_{a,O_2}

Table 6. – Time course of neurological and respiratory function (n=11)

	MRC score		Norris scale		VC % pred		FVC % pred		FEV1 % pred		FEV1/VC %		P_{a,CO_2} kPa		P_{a,O_2} kPa	
Pt	t_0	t_6	t_0	t_6	t_0	t_6	t_0	t_6	t_0	t_6	t_0	t_6	t_0	t_6	t_0	t_6
1	120	115	54	46	90	43	73	40	58	33	68	69	5.6	6.1	16.9	12.1
2	90	80	40	32	25	20	20	15	16	10	92	90	6.1	6.1	9.8	13.0
3	72	67	57	50	95	45	80	48	82	55	80	90	5.6	6.0	8.8	9.6
4	122	93	58	29	87	24	78	40	91	43	99	90	6.0	6.8	8.6	9.3
5	124	118	79	54	96	44	85	40	83	51	76	97	5.1	7.0	10.9	7.3
6	85	76	50	52	NA	NA	NA	NA	NA	NA	NA	NA	4.7	5.1	11.8	11.8
7	149	138	82	60	45	36	47	41	48	41	82	77	5.1	4.9	10.8	10.6
8	106	70	66	51	24	15	35	20	32	15	92	90	5.3	5.7	6.9	7.3
9	112	95	57	44	18	10	20	15	18	16	94	85	5.3	5.9	12.0	12.4
10	83	44	54	38	77	39	56	37	62	35	93	77	5.1	4.4	12.0	10.4
11	149	124	89	62	101	98	105	89	92	88	74	74	6.5	6.7	9.8	8.0
Mean	110	93	62	48	66	37	60	38	58	39	85	84	5.4	6.0	10.8	10.2
SD	26	29	15	11	34	25	29	21	29	23	10	9	0.5	0.8	2.6	2.0
p-value	<0.001		<0.0001		<0.04		<0.001		<0.001		NS		NS		NS	

Individual and mean values at t_0 and t_6 and means at t_6 are those of the 11 subjects available at t_6. NA: not available; Pt: patient; t_0: baseline value; t_6: 6 months follow-up value; MRC: Medical Research Council. For further definitions, see legend to table 4.

Table 7. – Time course of breathing pattern and mechanics (n=11)

	f_R breaths·min^{-1}		V_T/t_I mL·s^{-1}		t_I/t_{tot}		V'_E L·min^{-1}		V_T mL		f_R/V_T		P_{pl} cmH$_2$O		$C_{L,dyn}$ mL·cmH$_2$O^{-1}	
Pt	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6
1	10	16	214	214	0.39	0.39	5.0	6.7	500	420	20	38	9	10	150	143
2	22	31	125	122	0.40	0.41	6.6	9.3	300	300	73	103	6	6	140	120
3	17	17	151	147	0.42	0.43	6.5	4.4	380	260	45	65	6	7	130	100
4	14	23	197	147	0.38	0.51	6.3	3.4	450	150	31	153	5	4	98	85
5	25	38	163	157	0.51	0.53	12.5	7.6	500	200	50	190	5	6	44	40
6	25	23	225	160	0.34	0.48	11.5	2.3	460	100	54	230	6	16	31	79
7	16	15	145	142	0.46	0.47	6.4	5.4	400	360	40	42	13	8	75	39
8	13	22	208	198	0.40	0.42	6.5	3.3	500	150	26	147	13	10	100	93
9	26	26	130	124	0.41	0.43	8.3	9.1	320	350	81	74	3	2	105	87
10	11	18	417	417	0.32	0.32	8.8	5.0	800	280	14	64	7	4	150	75
11	15	16	183	179	0.41	0.42	6.8	8.0	450	500	33	32	6	5	120	130
Mean	18	23	198	183	0.40	0.44	7.8	5.7	461	279	42	104	7.2	7.1	104	90
SD	6	7	81	83	0.05	0.06	2.4	2.4	133	124	21	67	3.2	3.9	40	33
p-value	<0.01		NS		NS		NS		<0.01		<0.01		NS		NS	

Table 7. – (continued)

	$P_{0.1}$ cmH$_2$O		$P_{pl,max}$ cmH$_2$O		$P_{0.1}/P_{pl,max}$		$P_{0.1}/V_T/t_I$ cmH$_2$O·L·s^{-1}		PTP		PTI		WOB J·L^{-1}	
Pt	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6	*t*0	*t*6
1	2	2	44	27	0.05	0.07	9.3	9.3	152	140	0.10	0.14	0.65	0.91
2	3	3	35	26	0.09	0.11	24.0	22.9	141	110	0.08	0.09	0.50	0.98
3	2	3	32	10	0.06	0.30	13.2	20.0	150	140	0.07	0.30	0.66	0.87
4	2.5	1	40	30	0.06	0.03	12.6	6.8	186	170	0.04	0.06	0.30	0.29
5	1	3	31	20	0.03	0.15	3.0	3.2	105	250	0.08	0.14	0.20	0.34
6	4	6	36	20	0.11	0.30	8.2	17.1	167	334	0.08	0.26	0.84	1.93
7	4	1	40	33	0.10	0.03	27.5	7.0	231	149	0.14	0.11	1.19	0.56
8	2.5	3	35	20	0.07	0.15	12.0	15.1	189	210	0.15	0.21	0.89	0.79
9	1	1	45	10	0.02	0.10	15.3	16.1	200	250	0.03	0.08	0.99	0.98
10	1	1	25	15	0.04	0.07	2.4	2.3	112	78	0.12	0.09	0.57	0.48
11	1	1	36	25	0.03	0.04	5.5	5.5	174	112	0.10	0.10	0.61	0.44
Mean	2.18	2.2	36.3	21.4	0.06	0.12	12.08	11.39	164.3	176.6	0.09	0.14	0.67	0.78
SD	1.15	1.6	5.8	7.6	0.03	0.10	7.97	7.10	37.5	76.5	0.04	0.08	0.29	0.46
p-value	NS		<0.0001		<0.04		NS		NS		NS		NS	

Individual and mean values at *t*0 and *t*6 and means at *t*6 are those of the 11 subjects available at *t*6. For definitions, see legends to tables 4 and 6.

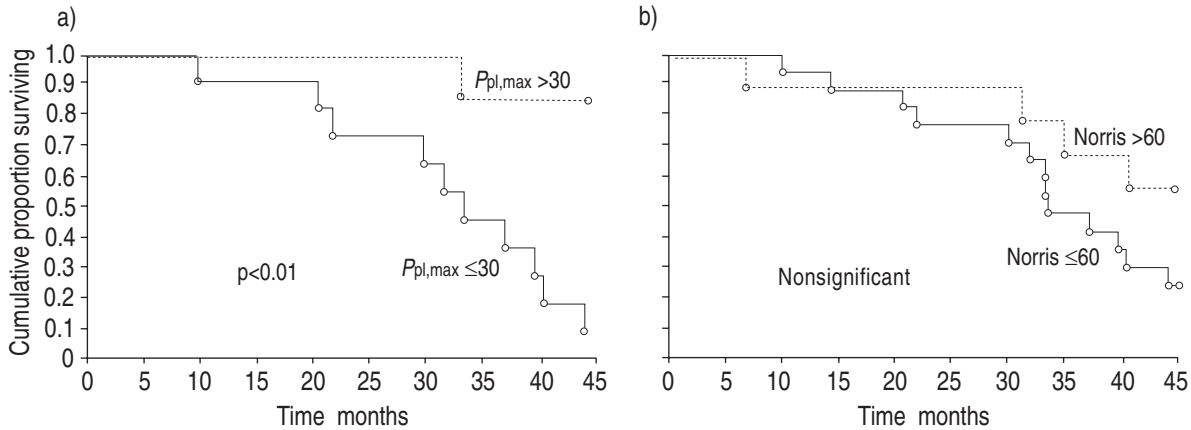

Fig. 1. – Cumulative survival rate according to: a) maximal oesophageal pressure ($P_{pl,max}$) and b) Norris score at presentation. $P_{pl,max}$ was measured in cmH$_2$O. For further explantation see the text.

<90% was 11±6% (range 3–82); the mean nadir value was 75±10% (range 54–88) and the mean number of desaturations was 3±2 (range 1–10).

Figure 1 shows the survival curve of patients according to the baseline values of $P_{pl,max}$ and Norris score. Patients with $P_{pl,max}$ <30 cmH$_2$O at presentation (16 out of 25 patients) showed a greater mortality in comparison to the patients with $P_{pl,max}$ >30 cmH$_2$O. During the same follow-up, 10 out of 25 patients who showed a Norris score ≤60 at presentation showed a higher mortality in comparison to the patients with a Norris score >60. Spearman rank correlation analysis showed that *t*0 $P_{pl,max}$ correlated with survival (months before deaths) (rho= 0.79, p<0.05). The same analysis showed that Norris

scale correlated as well (rho=0.64; p<0.05). A multivariate analysis excluding MRC and Norris scale showed that among all "respiratory", anthropometric and clinical history data, only age at the onset of disease predicted outcome (death *vs* survival) (73.7%); the older the patient at onset of disease, the worse the prognosis.

Discussion

This study suffered from a high rate of dropouts. Of the 38 patients referred, only 25 satisfied the acceptance criteria. Of these, only 11 patients had a repeat study at 6 months. The others either died or were unable to perform forced manoeuvres. The results of this study suggest a progressive deterioration of the breathing pattern and of the RM strength with progression of the disease, as revealed by the clinical score. Although most of our results could be predicted as consequences of RM weakness, as in other chronic neuromuscular diseases, and other investigators have evaluated pulmonary mechanics in patients with ALS [7, 8], the present study is more comprehensive and involves a larger number of patients than previous studies. ALS is a progressive degenerative disorder of the voluntary motor system that is characterized by loss and degeneration of motor neurons and their outflow tracts. The prognosis in ALS is extremely poor. Studies of 5 yr survival report rates ranging 18–42%, with 50% of patients dying in the first 3 yrs [22]. Our patients showed a 45 month survival rate of 24% with a mean survival time of 38 months and a large degree of intersubject variability.

Neurological impairment

To evaluate neurological impairment, we used the Norris scale, which, in its original or modified form, is the most widely used scoring system in ALS [14]. This scale was specifically developed to determine an objective index of the progression of the disease in clinical trials and for the assessment of drug efficacy. It includes self-reported ability to perform some activities (chewing, swallowing, dyspnoea) and observed impairment in neurological functions (speech, standing, walking) or data from objective examination (muscular and tongue hypertrophy). Recently, a number of more articulate scales have been proposed for monitoring ALS progression [6, 23–25].

Spirometry

Our patients showed a mild restrictive pattern; therefore, they may be considered as suffering from an initial respiratory involvement. Abnormalities in pulmonary function, including reduced FVC declining progressively over time, are reported [3–5, 26]. NAKANO *et al*. [27] were among the first to report serial pulmonary function studies in ALS. They measured spirometry and diffusing capacity in 25 patients, 9 months after onset and at 15, 22 and 33 months. Initial mean VC was within the normal range and averaged 58% pred at final measurement. RINGEL *et al*. [6] showed that the decline in pulmonary function as assessed by a megascore proposed by ANDRES *et al*. [24] most closely correlated with death. Thus, spirometry is considered of value, not only in detecting early respiratory involvement in ALS, but also in predicting the course of respiratory failure [5, 6]. Thirty one per cent of patients showed abnormalities of the maximal flow-volume loop consistent with upper airway dysfunction [28]. This finding was reported to occur often, but not exclusively, in patients with bulbar manifestations and seems to be unrelated to prognosis [29].

Arterial blood gases

Some patients develop hypercapnia at a relatively early stage of the disease, but, in general, hypercapnia is reported to occur as a preterminal event [7]. Our finding of hypercapnia in only 13% of cases is in keeping with literature showing that gas exchange is well maintained until loss of lung volume becomes very severe (FVC = 20% pred) [3, 5]. Breathing during sleep is commonly reported to be altered in many patients with other chronic neuromuscular disorders, even in patients such as ours who retain normal gas exchange during daytime; specifically, their pattern of breathing during sleep is fragmented with frequent episodes of hypopnoea and apnoea that are associated with hypercapnia and hypoxaemia [29]. Although formal sleep studies were beyond the aims of our study, noninvasive monitoring of night-time S_{a,O_2} in our patients is in keeping with these data. Oxygen desaturation leads to disrupted sleep with frequent arousals, daytime headaches and somnolence, as found in our patients.

Respiratory muscle function

Weakness of the RM is an obligatory component of ALS. Moreover, progression in ALS is faster than in most other chronic neuromuscular disorders, explaining why respiratory failure is the most common cause of death [7]. In patients with chronic RM weakness, VC has been reported to be correlated with RM strength, but reductions in VC are considered to be greater than anticipated for the degree of RM weakness [7, 30]. In our study, RM strength, as assessed by $P_{pl,max}$, was reduced. BLACK and HYATT [31] found that ALS patients with near normal VC, like the patients in the present study, often had significant decreases in maximal inspiratory and expiratory pressures, the grade of dyspnoea correlating with the degree of RM impairment. Our results seem to indicate that in ALS patients, reduction in RM strength as assessed by $P_{pl,max}$ may be observed at an early stage of respiratory involvement when lung volumes are still relatively preserved. On the other hand, although patients unable to perform respiratory manoeuvres were excluded by the study, RM strength as measured with a mouthpiece may be affected to a variable degree by the strength of facial muscles as opposed to that of the RM. This could explain, to some extent, the finding of a greater reduction of $P_{pl,max}$ than VC in our patients and confirm the usefulness of assessing RM strength in an early phase of the disease. Alternatively, the partial discrepancy between the reduction of $P_{pl,max}$

and VC could be also explained by a more reduced performance of the inspiratory muscle (IM) than of the expiratory muscles. In the absence of assessment of expiratory muscle function, this remains speculative. Furthermore, analysis showed that impairment of RM strength as assessed by $P_{pl,max}$ was a predictive factor of survival.

Breathing pattern and ventilatory drive

Patients with a more severe level of neurological involvement showed significantly reduced values of V_T with increased f_R/V_T ratio. Patients with RM weakness breathe faster and with a smaller V_T than healthy subjects [32]. Interestingly, P_{a,CO_2} changed only mildly over time despite a large reduction in V'_E (with a rapid shallow breathing observed at t_6), as in patients with a restrictive ventilatory defect of primary intrapulmonary origin [7]. $P_{0.1}$ and V_T/t_I ratio were not different from normal values. Measurement of $P_{0.1}$ and V_T/t_I ratio provide an estimate of central respiratory drive in such patients. It appears that the central respiratory drive is, in general, well preserved in patients with chronic neurological disorders [7, 32]. $P_{0.1}$ is an index that reflects both the neural drive to, and the resulting force output of, the IM [33]. Although $P_{0.1}$ is used as an index of neural output to IM in normal subjects, in patients with reduction in IM strength, $P_{0.1}$ absolute values may underestimate the effective neural drive. $P_{0.1}/P_{pl,max}$ ratio was used as an index of central respiratory output normalized for IM strength [34] and was found to be increased in patients in this study in comparison to healthy control subjects. $P_{0.1}/V_T/t_I$, an index of pulmonary impedance [35], was greater in patients than in controls and increased with time. Assessment of breathing pattern when using invasive devices, as well as using mouthpieces and noseclips, may have limitations. Nevertheless, our data show a reduction in V_T, while artifacts associated with invasive measurements lead to higher V_T and V'_E [36].

Respiratory mechanics

In our patients with more severe neurological involvement, PTI, also referred to as the tension time index (TTI), was found to be in the threshold range of diaphragmatic fatigue mainly due to reduced $P_{pl,max}$. With the limitations of the few patients studied in the follow-up, PTI did not worsen with time. BELLEMARE and GRASSINO [37] showed that a TTI of 0.15–0.18 may be considered a critical level for development of diaphragmatic fatigue while the TTI for accessory IM was reported to be 0.30 or smaller [38]. TTI can be found to be increased by any combination of increased resistance, decreased compliance, IM weakness and malnutrition [39]. PTP was not different from healthy control subjects. PTP has been shown to be an index of energy consumption of the IM indicating the patient's effort to breathe [40].

In conclusion, patients with amyotrophic lateral sclerosis with mild restrictive ventilatory pattern may show reduction in respiratory muscle function, rapid shallow breathing and a preserved neural drive. A severe reduction in inspiratory muscle strength is associated with a worse prognosis. The results of this study suggest a progressive deterioration of the breathing pattern and of the respiratory muscle strength with progression of the disease, as revealed by the clinical score.

Appendix

$C_{L,dyn}$ was calculated as follows:

$$C_{L,dyn} = V_T/(P_{tp1}-P_{tp2})$$

where V_T = tidal volume; P_{tp1} = transpulmonary pressure at maximum volume zero flow; P_{tp2} = transpulmonary pressure at minimum volume zero flow.

PTP was calculated with the following formula:

$$PTP = \int (P_{ee}-P_{oes}) + (Vol/C_{cw})) \, dt/t$$

where P_{ee} = end-expiratory oesophageal pressure; P_{oes} = current oesophageal pressure; Vol = current V_T; C_{cw} = chest wall compliance (estimated chest wall compliance equal to 200 $mL \cdot cmH_2O^{-1}$); dt = sample time; t = duration of breath in minutes.

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