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Thoracoabdominal asynchrony and paradoxical motion in middle stage amyotrophic lateral sclerosis

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ABSTRACT

Aim: To assess thoracoabdominal asynchrony (TAA) and the presence of paradoxical motion in middle stage amyotrophic lateral sclerosis (ALS) and its relationships with chest wall tidal volume ($V_{T,CW}$), breathing pattern and cough peak flow (CPF).

Methods: Phase angle (θ) between upper (RCp) and lower ribcage (RCa) and abdomen (AB), as well as percentage of inspiratory time for the lower ribcage (IP_{RCa}) and abdomen (IP_{AB}) moving in opposite directions were quantified using optoelectronic plethysmography in 12 ALS patients during quiet breathing and coughing. Paradoxical motion of the compartments was based on threshold values of θ and IP, obtained in twelve age and sex matched healthy persons.

Results: During quiet breathing, significantly higher RCa and AB θ ($p < .05$), IP_{RCa} ($p = 0.001$) and IP_{AB} ($p < 0.05$) were observed in ALS patients as compared to controls. In ALS patients, correlations between RCa and AB θ with forced vital capacity (FVC) ($r = -0.773$, $p < 0.01$), vital capacity ($r = -0.663$, $p < 0.05$) and inspiratory capacity (IC) ($r = -0.754$, $p < 0.01$), as well as between RCp and RCa θ with FVC ($r = -0.608$, $p < 0.05$) and CPF ($r = -0.601$, $p < 0.05$) were found. During coughing, correlations between RCp and AB θ with CPF ($r = -0.590$, $p < 0.05$), IC ($r = -0.748$, $p < 0.01$) and $V_{T,CW}$ ($r = -0.608$, $p < 0.05$), as well as between RCa and AB θ with CPF ($r = -0.670$, $p < 0.05$), IC ($r = -0.713$, $p < 0.05$) and peak expiratory flow ($r = -0.727$, $p < 0.05$) were also observed in ALS patients. ALS patients with paradoxical motion presented lower vital capacity and $FVC_{\%pred}$ ($p < 0.05$) compared to those without paradoxical motion.

Conclusions: Middle stage ALS patients exhibit TAA and paradoxical motion during quiet spontaneous breathing and coughing. In addition, diaphragmatic weakness (i.e. decrease in excursion of the RCa and AB compartments) was observed earlier in the lower ribcage rather than the abdominal compartment in this population.

1. Introduction

In healthy humans, the expansion and contraction of the ribcage and abdomen (AB) during spontaneous breathing occur synchronously with only little distortions (Allen et al., 1990; Ward et al., 1992). During inspiration, diaphragm contraction expands the abdominal ribcage (RCa), pushing the abdominal contents downward and the abdominal wall outward at the same time in which the intercostal and accessory muscles act to elevate and expand the pulmonary ribcage (RCp) (Zoumot et al., 2015). Thoracoabdominal asynchrony (TAA) is observed when uncoordinated motion between chest wall compartments occurs (Hammer and Newth, 2009).

TAA is primarily the result of disproportionate weakness of some respiratory muscles or discoordination between different muscle groups (Chihara et al., 1996), and is defined as the difference in expansion time or retraction between chest wall compartments (Allen et al., 1990). It is influenced by a variety of breathing patterns (Chihara et al., 1996; Crawford et al., 1983; Gilmartin and Gibson, 1984) and has already been identified in chronic obstructive pulmonary disease patients (Aliverti et al., 2009; Priori et al., 2013), asthma (Hillman et al., 1986;

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Ringel et al., 1983), preterm infants (Warren et al., 1997), tetraplegic (Mortola and Sant'Ambrogio, 1978) and stroke patients (Lima et al., 2014). People with neuromuscular disorders can also display TAA (Allen, 2010; Crescimanno et al., 2012; Diaz et al., 1993; Gibson et al., 1977) mainly due to reduced chest wall compliance (Diaz et al., 1993) and inspiratory muscle weakness (Hardart et al., 2002; Testa et al., 2005), resulting in a decreased contribution of chest wall compartments to tidal volume (Perez et al., 1996) and increased work of breathing (Testa et al., 2005).

With the progression of the disease, amyotrophic lateral sclerosis (ALS) patients display respiratory muscle weakness (Gregory, 2007; Lyall et al., 2001; Park et al., 2010), decreased tidal volume (Baydur, 1991; Vitacca et al., 1997) and cough peak flow (CPF) (Bach et al., 2008; Cleary et al., 2013; Senent et al., 2011), so it is possible that they also exhibit TAA and paradoxical motion. Thus, using optoelectronic plethysmography, an optical reflectance motion analysis system, we aimed to assess the within-breath TAA between the three different chest wall compartments, as well as the presence of paradoxical motion at rest during quiet breathing (QB) in middle stage ALS compared to age-matched healthy persons positioned at 45° trunk inclination. Secondly, as diaphragm contribution during QB and inspiration preceding coughing are determinants of cough efficiency in neuromuscular disease patients (Lo Mauro et al., 2010; LoMauro et al., 2014), we also assessed TAA and paradoxical motion during coughing as well as its relationships with chest wall volumes, breathing pattern and CPF.

2. Methods

2.1. Subjects

This is a cross-sectional study with a matched-pair design. Twelve ALS patients were recruited for the study, diagnosed according to the *El Escorial World Federation of Neurology* (Brooks et al., 2000) and classified as middle stage according to disease progression (Balendra et al., 2015; Roche et al., 2012; Simon et al., 2014) (see appendix tables A1 and A2), with forced vital capacity (FVC) < 80% of predicted, without bulbar dysfunction or tracheostomy, cardiovascular or pulmonary diseases, while those who could not adopt a 45° trunk inclination position were excluded. The control group consisted of twelve self-reported healthy persons matched by sex and age without any cardiovascular or respiratory disease and with spirometric values ≥ 80% of predicted.

The study was conducted within the confines of the World Medical Association Declaration of Helsinki for medical research involving human participants and approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte under number 1.344.512/2015. All individuals signed an Informed Consent Form.

2.2. Lung function and respiratory muscle strength

Lung function was assessed through a KoKo Digidoser® spirometer (nSpire Health, Longmont-EUA) with the subject seated in a standard chair. Assessments were carried out following the acceptability and reproducibility criteria (American Thoracic Society/European Respiratory, 2002), and the obtained values were compared to absolute and percentage of predicted spirometric values for the Brazilian population (Pereira et al., 2007).

A digital manometer (NEPEB-LabCare, Belo Horizonte-Brazil) was used to assess respiratory muscle strength by measuring maximal inspiratory (MIP) and expiratory pressures (MEP) starting from residual volume and total lung capacity, respectively. Moreover, absolute and percentage of predicted MEP/MIP ratio were calculated to assess the pattern of respiratory muscle strength loss in this population (Fregonezi et al., 2015). Sniff nasal inspiratory pressure (SNIP) was also used to assess inspiratory muscle strength (Heritier et al., 1994). For each of the above tests, the higher value obtained was compared to previous absolute and percentage values for the Brazilian population (Araujo et al., 2012; Neder et al., 1999) and considered for statistical analysis.

2.3. Functionality and clinical stage of the disease

The functionality of the ALS patients was assessed by a physician through the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (Gordon et al., 2004), validated for the Brazilian population (Guedes et al., 2010). The scale included items related to respiratory (maximum of 12 points) and bulbar function with a total score of 48 points (See appendix table A3).

2.4. Study design

All measurements were performed in one single day for each subject. After collecting lung function and respiratory muscle strength data, the patients were positioned in a standard bed at 45° trunk inclination in which the retro-reflective markers were placed and chest wall kinematics were recorded by TV cameras (see below) during: 1) 60 s of quiet spontaneous breathing at rest; 2) a vital capacity (VC) maneuver; and 3) a strong coughing maneuver (performed starting from total lung capacity).

2.5. Optoelectronic plethysmography

Optoelectronic plethysmography (BTS Bioengineering, Italy), a system described previously (Aliverti and Pedotti, 2003; Cala et al., 1996), enabled an assessment of chest wall kinematics. First, six TV cameras (three on the left and three on the right side of the subject), previously calibrated using a frequency of 60 frames·sec^{-1}, recorded the movement change of 52 retro-reflexive markers placed in specific anatomical points of the subjects' trunk surface in order to model the chest wall and its compartments – RCp, RCa and AB (Aliverti and Pedotti, 2003).

All markers were simultaneously visible to at least two TV cameras so that their three-dimensional positions and displacements could be reconstructed using stereo-photogrammetric methods by a motion analyzer (Ferrigno et al., 1994). A closed surface of the subject's total trunk was reconstructed by connecting the coordinates of the markers, and the breath-by-breath volume enclosed by this surface was computed by means of an algorithm based on the Gauss theorem (Cala et al., 1996). It is important to highlight that part of the chest wall surface in the supine position is hidden by the bed support, differently from the seated position in which 89 markers are placed on the anterior and posterior sides of the trunk. In this case, the posterior side of the trunk is then considered to be fixed and the geometrical chest wall model is built by considering a number of virtual points belonging to a reference plane that corresponds to the bed's horizontal surface (Aliverti et al., 2001, 2000).

The following parameters were obtained: Chest wall tidal volume ($V_{T,CW}$) and its compartments, CPF, VC, inspiratory capacity (IC), respiratory rate (RR), minute ventilation (VE), inspiratory time (Ti), expiratory time (Te), total time of the respiratory cycle (Ttot), mean inspiratory flow, mean expiratory flow and duty cycle. Rapid shallow breathing (RSB) was assessed according to Yang and Tobin (Yang and Tobin, 1991), and $\Delta V_{T,AB}/Ti$, $\Delta V_{T,RCp}/Ti$ and $\Delta V_{T,AB}/Te$ were calculated as the shortening velocity index of the diaphragm, inspiratory ribcage and expiratory muscles (Aliverti et al., 2002), respectively.

2.6. Chest wall asynchrony and inspiratory paradoxical movement

Firstly, the degree of asynchrony between chest wall compartments was obtained after constructing Lissajous figures (Aliverti et al., 2009; Allen et al., 1990) during QB and coughing. Phase angle (θ) between two volumetric signals was calculated and a graph was created by plotting two volumetric signals against each other. $\theta = \sin^{-1}(m/s)$ was used to define θ, where *m* was the ratio of the distance delimited by the

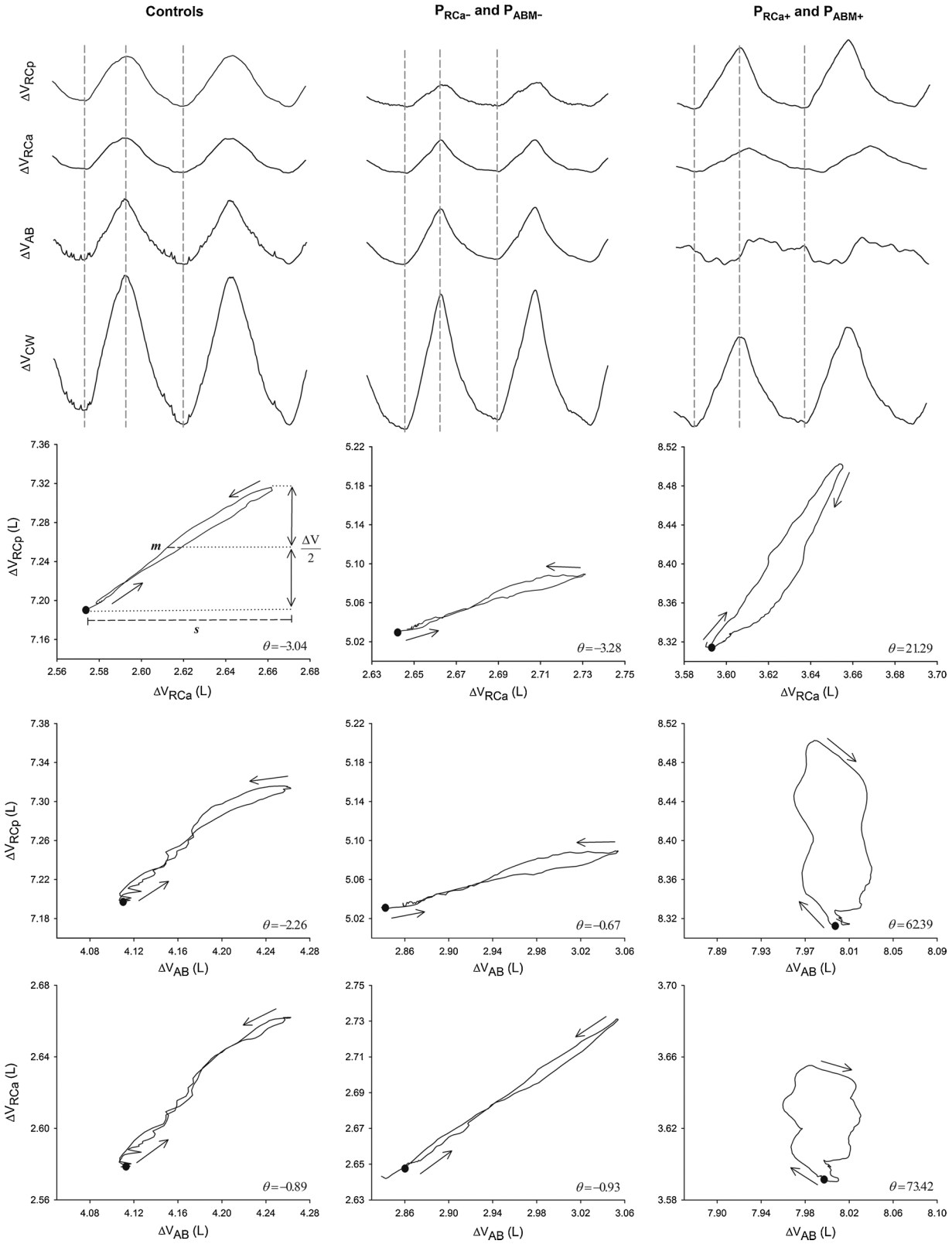

Fig. 1. Representative time-courses of the pulmonary rib cage (RCp) (y-axis), abdominal rib cage (RCa) (y-axis), abdomen (AB) (x-axis) and chest wall volumes of one healthy control subject (left), one middle stage amyotrophic lateral sclerosis subject with no paradoxical rib cage (P_{RCa}-) and abdominal (P_{AB}-) motion (middle), and one middle stage amyotrophic lateral sclerosis subject with paradoxical rib cage (P_{RCa}+) and abdominal (P_{AB}+) motion (right) according to the classification used in the study. L: Liters; Δ: Change; Arrows: Direction of the compartmental expansion; Black dot: Beginning of inspiration. m: line parallel to signal of the X-axis at 50% of the volume of the signal on the Y-axis; s: volume of the signal on the X-axis; θ: Phase angle.

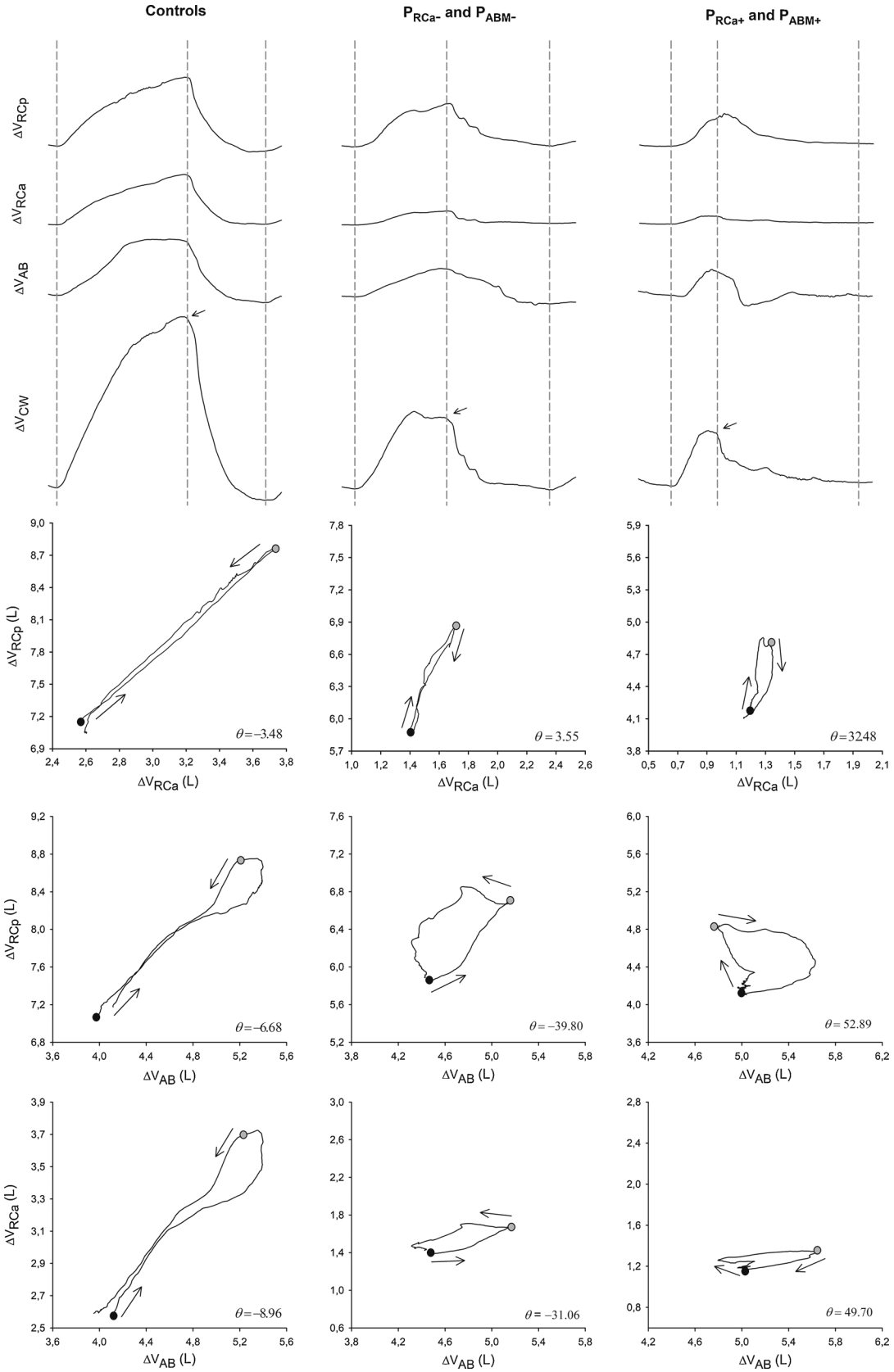

Fig. 2. Representative time-courses of the pulmonary rib cage (RCp), abdominal rib cage (RCa), abdomen (AB) and chest wall volumes of one healthy control subject (left), one middle stage amyotrophic lateral sclerosis subject with no paradoxical rib cage (P_{RCa}-) and abdominal (P_{AB}-) motion (middle), and one middle stage amyotrophic lateral sclerosis subject with paradoxical rib cage (P_{RCa} +) and abdominal (P_{AB} +) motion (right) according to the classification used in the study. Note in appendix table A3, patient number #3, that the subject with P_{RCa}- and P_{AB}- has no paradoxical abdominal motion according to the classification used in the study. L: Liters; Δ: Change; Small arrows: Start of cough; Big arrows: Direction of the compartmental expansion; Black dots: Start of inspiration; Grey dots; Start of cough; θ: Phase angle.

intercepts of the dynamic loop on a line parallel to the X-axis at 50% of the signal volume on the Y-axis, and *s* as the signal volume on the X-axis (Fig. 1). RCp (y-axis) *versus* RCa (x-axis), RCa (y-axis) *versus* AB (x-axis) and RCp (y-axis) *versus* AB (x-axis) loops during QB and coughing (Fig. 2) were calculated and a positive phase angle was interpreted as meaning that the expansion of the y-axis leads the x-axis (loop with clockwise direction); while a negative phase angle describes the reverse situation. A θ of zero represents a completely synchronous movement of the compartments, while 180° represents total asynchrony (Agostoni and Mognoni, 1966; Allen et al., 1990; Priori et al., 2013).

Secondly, inspiratory paradox time of RCa (IP_{RCa}) and AB (IP_{AB}) defined as the fraction of the inspiratory time in which the RCa and AB volumes decrease during inspiration (Aliverti et al., 2009), respectively, were also evaluated.

For data analysis, patients were subdivided into those presenting paradoxical movement of the RCa ($P_{RCa}+$) and AB ($P_{ABM}+$) compartments and those who did not (P_{RCa}- and P_{ABM}-, respectively). Grouping was based on upper and lower threshold values (defined as the 75th and 25th interquartile range, respectively) of θ and IP obtained at rest (mean of 15 breaths), and during a strong cough maneuver of all matched-paired healthy participants in this study. Thus, ALS patients were classified as presenting paradoxical movement if both θ and IP values exceeded the above-mentioned threshold points (i.e. RCp and AB θ and IP_{AB} for paradoxical ribcage motion, as well as RCp and Rca θ and IP_{RCa} for paradoxical ribcage motion).

3. Statistical analysis

Data are expressed as mean ± SD unless otherwise stated. Normality of data was assessed using the Shapiro-Wilk test. Differences between ALS patients and healthy persons regarding anthropometric, spirometric and respiratory muscle strength data, in addition to data obtained from optoelectronic plethysmography and asynchrony were tested using the paired *t*-test and Wilcoxon test for parametric and non-parametric data, respectively. Differences between subgroups were studied using the Mann-Whitney test. Relationships between the degree of asynchrony and both lung function and breathing pattern were studied using Pearson's *r* and Spearman's *rho* correlation coefficient.

No previous data were available to guide a sample size for this study. Thus, the power of the study as well as effect-sizes [Coefficients of determination (r^2) and Cohen's f^2 for parametric relationship analysis and Cohen's d for intergroup and subgroup non-parametric inferential analysis] (Cohen, 1988; Faul et al., 2009; Fritz et al., 2012) were calculated to avoid type II error by using G*Power software, version 3.1.9.2 (Kiel, Germany) (See appendix).

Inferential data analysis was performed using GraphPad Prism® software version 6.01 for Windows. A *p*-value of < 0.05 (2-sided) was considered as statistically significant for all statistical analyses.

4. Results

Data related to diagnosis criteria, onset region, clinical phenotype, the presence of familial ALS and cognitive impairment of all ALS included in the study are shown in appendix table A4. Anthropometric characteristics, spirometric, respiratory muscle strength and functionality data are shown in Table 1.

The main variable of the present study was selected to be the IP_{RCa}, since it is the first time that this parameter has been reported during coughing in the literature. Thus, a *post hoc* analysis considering the calculated effect size for this variable during coughing (Cohen's d = 0.96) presented a statistical power of (*1-ß*) = 0.99 for this study.

4.1. Cough peak flow, chest wall volumes, breathing pattern and velocity index of respiratory muscles

A significantly lower CPF ($p < 0.001$, Cohen's d = 1.26), VC ($p < 0.001$, Cohen's d = 1.92), IC ($p < 0.001$, Cohen's d = 1.89) and $V_{T,CW}$ ($p < 0.005$, Cohen's d = 1.29) were observed in ALS when compared to controls. Regarding compartmental analysis, significantly lower volumes in RCp ($p < 0.05$, Cohen's d = 0.77) and AB ($p < 0.05$, Cohen's d = 1.15) compartments were observed in ALS patients. Significantly lower Ti ($p = 0.001$, Cohen's d = 1.53), Te ($p < 0.05$, Cohen's d = 1.26) and Ttot ($p < 0.005$, Cohen's d = 1.43) as well as significantly higher RR ($p < 0.005$, Cohen's d = 1.50) and RSB ($p = 0.001$, Cohen's d = 1.77) were found in ALS patients when compared to controls (Table 2).

Table 1
Anthropometric, absolute and predicted values of lung function, respiratory muscle strength and functionality data of the subjects. Data presented as mean and standard deviation.

	Controls	ALS	*p* value
Subjects (n)	12	12	–
Age (years)	46.4 ± 12.2	46.4 ± 12.2	0.999
Height (m)	1.69 ± 0.1	1.66 ± 0.1	0.405
Weight (kg)	73.1 ± 13.1	64.8 ± 17.2	0.200
BMI (Kg/m^2)	25.4 ± 3.7	23.3 ± 5.2	0.253
FVC (L)	4.21 ± 0.73	2.17 ± 0.85	< 0.001
FVC (%pred)	99.93 ± 8.2	53.3 ± 18.6	< 0.001
FEV_1 (L)	3.42 ± 0.55	1.63 ± 0.59	< 0.001
FEV_1 (%pred)	100.2 ± 8.8	49.2 ± 13.4	< 0.001
FEV_1 /FVC	0.81 ± 0.01	0.81 ± 0.02	0.567
FEV_1 /FVC (%pred)	81 ± 1.8	81.4 ± 2.9	0.678
$FEF_{25-75\%}$	3.44 ± 0.97	1.48 ± 0.70	< 0.001
PEF (L/s)	7.39 ± 1.75	3.02 ± 1.54	< 0.001
MIP (cmH_2O)	119.8 ± 26.04	33.25 ± 10.86	< 0.001
MIP (%pred)	113.5 ± 15.7	33.6 ± 10.1	< 0.001
MEP (cmH_2O)	138.8 ± 29.22	46.17 ± 22.09	< 0.001
MEP (%pred)	125.4 ± 24.1	44.3 ± 18.4	< 0.001
MEP/MIP (cmH_2O)	1.04 ± 0.10	1.01 ± 0.06	0.476
MEP/MIP (%pred)	1.11 ± 0.20	1.38 ± 0.60	0.141
SNIP (cmH_2O)	130.9 ± 26.96	33.75 ± 9.5	< 0.001
SNIP (%pred)	123.8 ± 18	39.1 ± 8.4	< 0.001
ALSFRS-R	–	26.67 ± 8.31	–
Respir. subscore	–	10.08 ± 1.56	–

FVC: Forced Vital Capacity; FEV1: Forced expiratory volume in the 1 st second; FEV1/FVC: Ratio of forced expiratory volume in the first second to forced vital capacity; FEF25-75%: Forced expiratory flow at 25–75%; PEF: Peak expiratory flow; MIP: Maximum inspiratory pressure; MEP: Maximum expiratory pressure; MEP/MIP: Ratio between maximum inspiratory and expiratory pressures; SNIP: Sniff nasal inspiratory pressure; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-revised; n: number of subjects; m: meters; kg: kilograms; L: Liters; %pred: Percentage of predicted; L/s: Liters per second; cmH_2O: centimeters of water.

4.2. Thoracoabdominal asynchrony during coughing and quiet breathing

No differences were found in θ between groups during coughing, however significant differences in IP_{RCa} ($p < 0.005$, Cohen's d = 0.96) were observed (Table 3). In addition, significant correlations between RCp and AB θ with CPF ($r = -0.590$, $p < 0.05$, $r^2 = 0.35$, Cohen's $f^2 = 0.53$), PEF ($r = -0.727$, $p < 0.01$), IC ($r = -0.748$, $p < 0.01$) and $V_{T,CW}$ ($r = -0.608$, $p < 0.05$, $r^2 = 0.37$, Cohen's $f^2 = 0.58$); RCa and AB θ with CPF ($r = -0.670$, $p < 0.05$, $r^2 = 0.45$, Cohen's $f^2 = 0.81$), IC ($r = -0.713$, $p < 0.05$) and PEF ($r = -0.727$, $p < 0.05$); and RCp and RCa θ with RR ($r = 0.638$, $p < 0.05$) were observed in ALS patients.

During QB, significant differences in RCp and AB θ ($p < 0.05$, Cohen's d = 0.54) and RCa and AB θ ($p < 0.05$, Cohen's d = 0.62) were found in ALS when compared to controls (Table 3). In addition, a significantly higher IP_{RCa} ($p = 0.001$, Cohen's d = 2.03) and IP_{AB} ($p < 0.05$, Cohen's d = 0.53) were found in ALS patients (Fig. 3), as well as a significant correlation between RCp and AB θ and FVC ($r = -0.773$, $p < 0.01$), VC ($r = -0.663$, $p < 0.05$) and IC ($r = -0.754$, $p < 0.01$); RCp and RCa θ and FVC ($r = -0.608$, $p < 0.05$) and CPF

Table 2
Cough peak flow, vital capacity, chest wall compartmental volumes, breathing pattern and shortening velocity index of respiratory muscles. Data presented as mean and standard deviation.

	Controls	ALS	*p* value
Subjects $_{(n)}$	12	12	–
CPF $_{(L/s)}$	8.452 ± 3.35	4.618 ± 2.50	< 0.001
VC $_{(L)}$	4.278 ± 1.39	1.958 ± 0.70	< 0.001
IC $_{(L)}$	3.491 ± 1.03	1.795 ± 0.54	< 0.001
$\Delta V_{T,CW}$ $_{(L)}$	0.619 ± 0.24	0.342 ± 0.07	< 0.005
$\Delta V_{T,RCp}$ $_{(L)}$	0.182 ± 0.13	0.089 ± 0.03	< 0.05
$\Delta V_{T,RCa}$ $_{(L)}$ ‡	0.105 ± 0.05	0.065 ± 0.02	0.059
$\Delta V_{T,AB}$ $_{(L)}$	0.334 ± 0.14	0.186 ± 0.08	< 0.05
Ti $_{(s)}$	1.68 ± 0.45	1.08 ± 0.28	0.001
Te $_{(s)}$	2.43 ± 0.69	1.66 ± 0.43	< 0.05
Ttot $_{(s)}$	4.12 ± 1.10	2.74 ± 0.70	< 0.005
RR $_{(bpm)^{-1}}$	15.73 ± 4.30	23.62 ± 5.84	< 0.005
VE $_{(L/min)^{-1}}$	9.17 ± 2.71	7.99 ± 2.76	0.261
Duty cycle	41.18 ± 3.83	39.63 ± 3.02	0.329
RSB	30.50 ± 16.99	73.08 ± 27.52	0.001
$\Delta V_{T,CW}$/Ti $_{(L/s)^{-1}}$	0.375 ± 0.11	0.343 ± 0.13	0.481
$\Delta V_{T,CW}$/Te $_{(L/s)^{-1}}$	0.263 ± 0.08	0.222 ± 0.07	0.177
$\Delta V_{T,RCp}$/Ti $_{(L/s)}$	0.107 ± 0.05	0.088 ± 0.04	0.374
$\Delta V_{T,AB}$/Te $_{(L/s)}$	0.140 ± 0.05	0.118 ± 0.05	0.403
$\Delta V_{T,AB}$/Ti $_{(L/s)}$	0.162 ± 0.08	0.186 ± 0.10	0.408

CPF: Cough peak flow; VC: Vital capacity; IC: Inspiratory capacity; $V_{T,CW}$: Chest wall volume; $V_{T,RCp}$: Pulmonary ribcage volume; $V_{T,RCa}$: Abdominal ribcage volume; $V_{T,AB}$: Abdominal volume; Ti: Inspiratory time; Te: Expiratory time; Ttot: Total time of the respiratory cycle; RR: respiratory rate; VE: Minute volume; RSB: Rapid shallow breathing: $\Delta V_{T,CW}$/Ti: Mean inspiratory flow; $\Delta V_{T,CW}$/Te: Mean expiratory flow; $\Delta V_{T,RCp}$/Ti: Shortening velocity index of inspiratory ribcage muscles; $\Delta V_{T,AB}$/Ti: Shortening velocity index of diaphragm; $\Delta V_{T,AB}$/Te: Shortening velocity index of expiratory muscles; ‡ non-parametric data distribution; L: Liters; min: minutes; s: seconds; L/s: Liter per second; Bpm: Breaths per minute.

Table 3
Thoracoabdominal asynchrony during quiet breathing and coughing.

	During quiet breathing		During cough	
	Controls	ALS	Controls	ALS
Subjects $_{(n)}$	12	12	12	12
θ RCpxAB °	−6.622 [−8.67 – −3.03]	−0.702 [−7.78 – 5.11]*	7.370 [−7.52 – 11.08]‡	10.250 [−17.02 – 35.22]
θ RCaxAB °	−2.556 [−6.42 – −0.29]	2.135 [−2.88 – 9.04]*	3.045 [−6.62 – 8.72]‡	10.290 [−16.24 – 28.50]
θ RCpxRCa °	−4.034 [−10.48 – −1.47]‡	−3.765 [−13.89 – −1.88]	1.455 [−5.20 – 8.39]‡	1.715 [−4.29 – 11.81]

Data presented as median and interquartile range between 25–75%. RCp: Pulmonary ribcage; RCa: Abdominal ribcage; AB: Abdominal; θ: Phase angle; °: Degrees; %: Percentage. ‡ parametric data distribution; * < 0.05 versus controls.

(r = –0.601, $p < 0.05$) and RCa and AB θ with RSB (r = 0.645, $p < 0.05$).

4.3. Paradoxical abdominal motion during coughing and quiet breathing

The upper and lower limits for RCp and AB θ during coughing were determined as 7.52° and −11.08°, respectively; and the upper limit for IP_{AB} was defined as 12.09%. $P_{ABM}+$ was observed in 5 patients with ALS. Of the 7 remaining patients (P_{ABM}-), only two showed no evidence of paradoxical motion by either criterion, while 4 showed abnormal θ and 1 abnormal IP_{AB}. No statistically significant differences between those with and without paradoxical abdominal motion during coughing were found.

The upper and lower limits for RCp and AB θ during QB were -1.87° and -10.48°, respectively; while the upper limit for IP_{AB} was 8.59%. $P_{ABM}+$ was observed in 6 patients. Of the 6 patients with P_{ABM}-, 2 patients showed IP_{AB} values above the threshold, 3 showed abnormal θ and 1 showed no evidence of paradoxical motion by either criterion (See appendix tabel A5). During QB a significant higher $MEP/MIP_{\%pred}$ ratio ($p < 0.01$, Cohen's d = 2.51) was found in $P_{ABM}+$ when compared to P_{ABM}- [median of 1.72 (1.46–2.38) and 0.91 (0.79–1.07), respectively].

4.4. Paradoxical ribcage motion during coughing and quiet breathing

During coughing, the upper and lower limits for RCp and Rca θ were determined as 5.20° and -8.39°, respectively; and the upper limit for IP_{RCa} was defined as 3.30%. $P_{RCa}+$ was observed in 6 patients. Of the 6 patients showing P_{RCa}-, only one showed no evidence of paradoxical motion by either criterion, while 5 patients showed abnormal IP_{RCa}. A significantly lower $FVC_{\%pred}$ ($p < 0.05$, Cohen's d = 1.26) was observed in $P_{RCa}+$ [median of 42 (28.8–55.6)], when compared with P_{RCa}- subgroup [median of 62.6 (50.9–72.6)] during coughing, as well as higher $\Delta V_{T,RCp}$/Ti [median of 0.10 (0.08-0.15) *vs* 0.06 (0.05-0.07) L/sec^{-1}, $p < 0.01$, Cohen's d = 1.67].

During QB, the upper and lower limits for θ were, -3.03° and -8.67°, respectively, while the upper limit for IP_{RCa} was 6.95%. $P_{RCa}+$ was observed in 6 patients, while it was not for the remaining 6. Of these, 5 patients showed IP_{RCa} values above threshold and 2 showed no evidence of paradoxical motion by either criterion (See appendix table A6). A significantly lower FVC [median of 1.59 (0.89–2.32) *vs* 2.66 (2.39–2.91) L, p < 0.05, Cohen's d = 1.58], $FVC_{\%pred}$ [median of 37 (28.8–46) *vs* 62.6 (56–72.6), p < 0.01, Cohen's d = 2.35], FEV_1 [median of 37.4 (29.7–44) *vs* 59.5 (51–61.4) p < 0.01, Cohen's d = 2.14] and VC [median of 1.47 (0.98–2.17) *vs* 2.34 (1.94–2.70) p < 0.05, Cohen's d = 1.46] were observed in $P_{RCa}+$ when comparing with P_{RCa}-, respectively.

5. Discussion

5.1. Main findings

The main findings of the study were that middle stage ALS patients positioned at 45° trunk inclination a) Display greater TAA between the upper ribcage compartments and AB during QB when compared to controls, and the magnitude of this TAA is negatively related to forced vital capacity, inspiratory capacity and vital capacity; b) During coughing, TAA is negatively related to cough peak flow, peak expiratory flow, inspiratory capacity and chest wall tidal volume; c) Paradoxical abdominal and ribcage motion can be observed in middle stage ALS patients at rest and during coughing; d) ALS patients with paradoxical motion exhibit a decreased VC, FVC and FEV_1 as well as increased $MEP/MIP_{\%pred}$ ratio and $\Delta V_{T,RCp}$/Ti.

5.2. Thoracoabdominal asynchrony

TAA is clinically useful in evaluating airflow obstruction in infants (Allen et al., 1990), early-onset hyperinflation and dyspnoea in chronic obstructive pulmonary disease (Aliverti et al., 2009; Priori et al., 2013), as well as in estimating pulmonary function and efficiency of mechanical ventilation in Duchenne muscular dystrophy (Diaz et al., 1993) and spinal muscular atrophy (Hardart et al., 2002; Testa et al., 2005). According to Allen (Allen, 2010), TAA is a consequence of weakness and inefficiency of respiratory muscles in neuromuscular disease patients leading to a decrease in V_{CW}, increased work of breathing (Mortola and Sant'Ambrogio, 1979), and consequently increased respiratory muscle loading and thus increased risk of respiratory muscle fatigue (Diaz et al., 1993).

A significantly higher TAA between RCp and AB as well as between

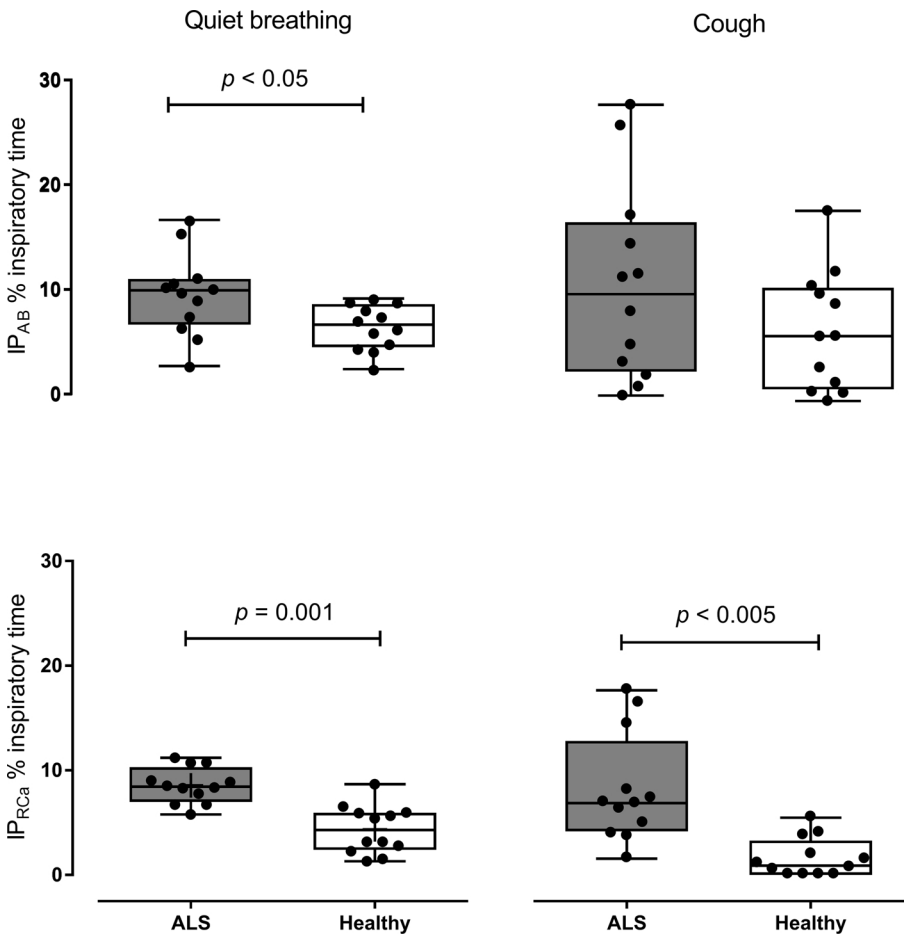

Fig. 3. Box plots showing the inspiratory paradox time of abdominal rib cage (IP_{RCa}) and abdomen (IP_{AB}) during quiet breathing and coughing. Center lines indicate the median and plus signs show mean values. The upper and lower limits of each box represent the 75th and 25th percentiles, respectively. Whiskers denote minimum and maximum values. Black dots represent each patient individually. %: Percentage; ALS: Amyotrophic Lateral Sclerosis.

RCa and AB were observed in ALS when compared to controls during QB. These findings are in agreement with other studies performed in neuromuscular disease (Diaz et al., 1993; Perez et al., 1996), and although no correlations with respiratory muscle strength were found, it is likely to be associated with the weakness and inefficiency of the diaphragm (Allen, 2010). In the early stages of ALS, the intercostal and accessory muscles assume the primary role in decreasing intrathoracic pressure and increasing ventilation during spontaneous breathing, leading to a paradoxical inward abdominal motion and decreased tidal volume (Higenbottam et al., 1977; Kreitzer et al., 1978; Romer et al., 2017; Similowski et al., 2000). In our study, this notion is supported by a significantly higher IP_{AB} and IP_{RCa}, showing that both compartments move in opposite directions in relation to the RCp expansion during inspiration. The former can be explained by the failure of the diaphragm opposing the decreasing intrathoracic pressure, and consequently increasing transdiaphragmatic pressure, being compensated by an expansion of the RCp promoted by the intercostal and accessory muscles (Allen, 2010; Diaz et al., 1993; Similowski et al., 2000); in addition to the latter due to the fact that the part apposed to the diaphragm (RCa) may possibly be influenced by the inward motion of the abdomen during inspiration due to the insertional expiratory muscle component (rectus abdominis and external and internal obliquus) (De Troyer et al., 1983; Mier et al., 1985).

In infants, Allen et al. (Allen et al., 1991) and Stromberg and Nelson (Stromberg and Nelson, 1998) observed that TAA during sleep was positively related to the severity of abnormalities in pulmonary resistance and negatively related to compliance, suggesting that the quantification of TAA could provide a useful indicator for infant respiratory function. In ALS patients, respiratory compliance is reduced and negatively related to FVC and respiratory muscle weakness (Lechtzin et al., 2006). Although we did not measure compliance in our patients, we have shown for the first time that the degree of TAA during QB is negatively related to FVC, VC, IC and PCF and positively related to RSB in middle stage ALS patients, thus suggesting that TAA reflects lung restriction while also being related to the generation of insufficient volume prior to coughing in this population (LoMauro et al., 2014).

During coughing, Lanini et al. (Lanini et al., 2007) observed that differences in muscle force acting on upper and lower ribcages result in substantial ribcage distortion in healthy persons. In neuromuscular disease, insufficient deflation of chest wall compartments in addition to ribcage distortion result in cough ineffectiveness (Lanini et al., 2008). Although we measured θ during coughing instead of distortion, our results suggest an imbalance between compartments, probably because of different compartmental pressures and elastic and resistive forces during the expulsive maneuver (Allen, 2010). Moreover, the negative relationships between RCp and AB θ, as well as RCa and AB θ, with CPF, PEF, IC and $V_{T,CW}$ are in agreement with Lanini et al. (Lanini et al., 2007, 2008) and LoMauro et al. (LoMauro et al., 2014), and may be explained by a delayed or slower activation of the diaphragm (LoMauro et al., 2010) and abdominal muscles (Perez et al., 1996) which contributes to generating insufficient inspiratory volume previous to coughing (Smith et al., 2012) and expiratory pressure (De Troyer and Estenne, 1995), respectively, thus decreasing cough effectiveness (LoMauro et al., 2014).

5.3. Paradoxical motion

To our knowledge, this is the first study in which paradoxical ribcage and abdominal motion during coughing and QB have been quantified in ALS patients. Accurate estimation of chest wall volume and motion by surface measurements using optoelectronic plethysmography enabled an assessment of TAA between the two ribcage

subcompartments (RCp - the part apposed to the lung; and RCa - the part apposed to the diaphragm) and AB (Aliverti et al., 2009; Zoumot et al., 2015), thus differing from studies using respiratory inductance plethysmography in which chest wall was composed of two compartments (Allen et al., 1990; Diaz et al., 1993; Perez et al., 1996).

In ALS patients, diaphragm impairment is present and may be due to several factors including the loss of cortico-respiratory pathways (Shimizu et al., 2010) and deterioration of motor cortex pathways (Miscio et al., 2006), progressive reduction of diaphragm action potentials and motor unit recruitment, phrenic nerve fiber loss and diaphragm atrophy (Llado et al., 2006). Previous studies (Higenbottam et al., 1977; Kreitzer et al., 1978) have shown that people with diaphragmatic dysfunction display paradoxical abdominal motion. In this case, inspiration relies primarily on the intercostal and accessory muscles, drawing the diaphragm into the chest wall due to its decreased activation (Hammer and Newth, 2009; Similowski et al., 2000).

In our study, patients classified as $P_{ABM}+$ during QB exhibited a significantly higher $MEP/MIP_{\%pred}$ ratio indicating an imbalance between respiratory muscle strength and also suggesting that MIP is the first to be impaired in middle stage ALS (Fregonezi et al., 2015). On the other hand, when subdividing patients in $P_{RCa}+$ and P_{RCa-} during coughing and QB, it was observed that $P_{RCa}+$ patients exhibited a lower VC, FVC (in absolute and percentage of predicted values) and FEV_1, as well as a higher $\Delta V_{T,RCp}/Ti$ when compared to P_{RCa-} patients. These results can be explained by a lower chest wall compliance and lung elastance (Lechtzin et al., 2006), as well as reduced ventilatory efficiency (Orsini et al., 2015) and respiratory muscle performance (Kang and Bach, 2000; Park et al., 2010), which may lead to a decrease in two predictive biomarkers for survival in ALS; the strength of the diaphragm contraction (Polkey et al., 2017) and VC (Carrié et al., 2016). In addition to the progression of the disease, the increased $\Delta V_{T,RCp}/Ti$ may tend to compensate for the decreased $V_{T,CW}$ and maintain VE through recruitment of ribcage and accessory muscles during inspiration (Diaz et al., 1993; Mortola and Sant'Ambrogio, 1978; Perez et al., 1996; Romer et al., 2017; Similowski et al., 2000).

Our results demonstrate that TAA may influence FVC, $V_{T,CW}$ and CPF in middle stage ALS patients. Secondly, it was also observed that RCp expansion initiates first in this population, then expansion of the RCa and AB compartments when positioned at 45° trunk inclination, being consistent with increased thoracic muscle effort (Hammer and Newth, 2009) and/or a weakened diaphragm (Goldman et al., 1993) (i.e. delayed diaphragm activation and inability to produce a maximal inspiration prior to coughing). These features also suggest that diaphragm function is impaired prior to the muscles of the upper ribcage (Polkey et al., 2017; Romer et al., 2017) and this is clearly observed in the lower ribcage compartment rather than the abdomen. In addition, these findings are in agreement with Similowski et al. (Similowski et al., 2000), who showed that paradoxical abdominal motion measured by two mechanical strain gauges was related to diaphragm impairment in ALS patients, and compensated by an increase in inspiratory neck muscles activity. Moreover, our results are also in agreement with those of Layton et al. (Layton et al., 2016) who used optoelectronic plethysmography and recently observed that ALS patients with a weakened diaphragm have a paradoxical motion pattern of the lower ribcage.

5.4. Study strengths and limitations

This study has some limitations. Firstly, the sample size was small and TAA was only assessed at 45° trunk inclination. It is known that the supine position by itself has an effect on breathing mechanics (i.e. weight of abdominal content upon the diaphragm that increases intra-abdominal pressure and lengthens the diaphragm's fibers, thereby modifying the ability to generate a given trans-diaphragmatic pressure, limiting the costal movement during inspiration due to the weight of the thorax, changes in inspiratory muscle action distribution and mechanics with muscles of the ribcage acting mainly on its lateral sides) (Mortola and Anch, 1978; Vellody et al., 1978; Ibanez and Raurich, 1982; Vilke et al., 2000), thus the effects of other postures on TAA during coughing need to be properly addressed in future studies. Secondly, OEP data were not acquired during the MIP, MEP and SNIP measurements. Thirdly, there was an absence of hemodynamic and transdiaphragmatic pressure monitoring and we also did not measure FVC in prone and supine positions. However, it is important to highlight the use of the optoelectronic plethysmography in detecting the early signs of respiratory muscle impairment in the neuromuscular population. As shown in this study, minimal collaboration was required from the patients during both quiet breathing and coughing, and accurate assessments were performed with no interference from nose clips, mouth-pieces, face masks or invasive techniques which may alter mouth and cheek movements and the respiratory system response.

6. Conclusion

We have shown evidence that middle stage ALS patients exhibit TAA and paradoxical motion during quiet spontaneous breathing and coughing. These factors were also related to changes in forced vital capacity, cough peak flow, peak expiratory flow, inspiratory capacity, chest wall volumes and breathing pattern. In these patients, diaphragmatic weakness can be observed earlier in the lower ribcage compartment rather than the abdomen via optoelectronic plethysmography.

Ethical approval: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of interest

The authors declare they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resp.2018.06.012.

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