Spirometry in the Supine Position Improves the Detection of Diaphragmatic Weakness in Patients With Amyotrophic Lateral Sclerosis*

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Study objectives: **To determine which respiratory function tests best predicted diaphragmatic strength in patients with amyotrophic lateral sclerosis.**
Patients and methods: **Patients referred for pulmonary evaluation were included (n = 25) if they underwent measurement of transdiaphragmatic pressure (Pdi) and one or more of the following on the same day: upright FVC, supine FVC, upright FEV_1, supine FEV_1, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and $PaCO_2$. Abdominal paradox and use of accessory muscles were also assessed. Bivariate analyses were performed using simple linear regression. Sensitivity and specificity of the potential predictors to detect an abnormal Pdi (< 70 cm H_2O) were calculated.**
Setting: **Pulmonary function laboratory of an academic medical center.**
Results: **Upright FVC, FEV_1, and MEP were all significantly correlated with Pdi, while MIP and $PaCO_2$ were not. Supine FVC was the most highly correlated predictor of Pdi (R^2 = 0.76). A cutoff of supine FVC that was < 75% predicted was 100% sensitive and specific for predicting an abnormally low Pdi. Accessory muscle use and abdominal paradox were both significantly associated with Pdi, and the presence of accessory muscle use had a sensitivity of 84% and a specificity of 100% for detecting a low Pdi.**
Conclusions: **Our findings suggest that supine FVC is an excellent and simple test of diaphragmatic weakness.** ***(CHEST 2002; 121:436–442)***

Key words: amyotrophic lateral sclerosis; diaphragm strength; pulmonary function tests; respiratory muscles; spirometry; transdiaphragmatic pressure

Abbreviations: ALS = amyotrophic lateral sclerosis; BMI = body mass index; ΔFVC = change in FVC from upright to supine; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; Pdi = transdiaphragmatic pressure; Pdi-sniff = transdiaphragmatic pressure during maximal sniffing; Pes = esophageal pressure

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease. Respiratory muscles atrophy over the course of the disease, leading to respiratory failure.[1–3] Though ALS is uniformly fatal, the rate of progression varies widely between patients.[1] One clinically relevant prognostic factor in patients with ALS is the timing of onset of respiratory muscle weakness. Patients with respiratory muscle weakness as the initial manifestation of ALS have very poor prognoses, with median survival from diagnosis of only 2 months.[1] It is crucial, therefore, to accurately detect respiratory muscle involvement in order to estimate prognosis, provide patient counseling, and make treatment decisions.

The diaphragm is the primary inspiratory muscle, and assessment of transdiaphragmatic pressure (Pdi) is the "gold standard" measure of diaphragmatic strength.[4] Esophageal pressure (Pes) is a measure of global inspiratory strength that closely parallels Pdi.[5] Pes has been shown to closely correlate with survival in patients with ALS.[6] Unfortunately, measurement

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of Pdi and Pes are invasive, labor-intensive tests that are not performed at many centers. Additionally, patients may be reluctant to undergo invasive testing repeatedly, making Pdi and Pes impractical for serial measurement.

Common measures of respiratory status in ALS patients include maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), $Paco_2$, and FVC.[7] MIP and MEP are technically difficult to perform, even in healthy volunteers. Maximal respiratory efforts against an occluded airway are demanding and unpleasant, often leading to falsely low results.[8,9] This is especially true of ALS patients with facial muscle weakness who are unable to form an airtight seal around a mouthpiece. Hypercarbia ($Paco_2 > 45$ mm Hg) is a late finding in respiratory failure from neuromuscular disease[10] but can be present in patients with normal muscle strength due to other conditions, such as obstructive lung disease or central hypoventilation. Most authorities recommend initiating noninvasive ventilatory support when the FVC falls to $< 50\%$ of the predicted value,[11] but patients can have moderate or severe diaphragmatic weakness before the vital capacity reaches this point.[12]

We analyzed pulmonary function test results in patients with ALS in order to determine the best predictors of Pdi during maximal sniffing (Pdi-sniff), and to determine if a noninvasive measure could feasibly replace assessment of Pdi-sniff in clinical practice. We had several study hypotheses, including: (1) upright FVC alone is not sufficiently sensitive nor specific to detect the onset of diaphragmatic weakness; (2) MIP is a nonspecific test of diaphragmatic weakness; (3) $Paco_2$ is poorly correlated with Pdi-sniff; (4) the change in FVC from upright to supine (ΔFVC) is more closely correlated with Pdi-sniff than upright FVC alone; and (5) physical examination findings of abdominal paradox and or accessory muscle use can provide useful information in the diagnosis of diaphragmatic weakness. No previous study has compared supine spirometry with Pdi in a group of ALS patients.

Materials and Methods

Study Population

All ALS patients referred for pulmonary evaluation at a single academic medical center between December 1995 and June 2000 were considered for analysis. Patients were evaluated by neurologists and met the El Escorial definition of definite or probable ALS.[13] Eligible patients had Pdi-sniff measured and at least one of the following tests performed on the same day: upright spirometry, supine spirometry, MIP, MEP, and $Paco_2$. Pulmonary function tests were ordered for clinical indications, not as part of a study protocol. Some patients had serial pulmonary function tests performed, but no patient had Pdi-sniff measured more than once. Bulbar dysfunction was graded as either present or absent based on the presence of speech changes or difficulty swallowing as reported by patients. The study was approved by the Johns Hopkins Joint Committee on Clinical Investigation.

Pulmonary Function Testing

All tests were performed in the Johns Hopkins Hospital pulmonary function laboratory and met or exceeded applicable standards of the American Thoracic Society.[14] Spirometry was performed in the upright-seated position and in the supine position. Predicted values were based on the formulas of Goldman and Becklake.[15] Because there are no reference standards for supine FVC, percent of predicted supine FVC was calculated using predicted values for upright FVC. MIP and MEP were measured in the seated position using a standard flanged mouthpiece. A 1-mm $\times$ 15-mm leak was present distal to the mouthpiece to prevent participation of the orofacial muscles. MIP was measured from residual volume, and MEP was measured from total lung capacity. Pdi was measured by maximal sniff from functional residual capacity following the protocol of Miller et al.[16] Two balloon catheters were inserted via the nares and advanced fully and connected to differential pressures transducers (Gould Electronics; Oxnard, CA). The esophageal balloon was gradually withdrawn from the stomach until the gastroesophageal junction was identified, and it was then withdrawn an additional 10 cm. Prior to August 1999, catheters were custom-made in the Johns Hopkins pulmonary laboratory; after August 1999, they were manufactured by Ackrad Labs, Crawford, NJ. Nineteen study patients had Pdi measured prior to changing catheter manufacturers. Analyses were carried out to compare whether the change in catheters altered the results. These demonstrated similar findings with both catheter types. Patients were instructed to make sharp, maximal sniffs from functional residual capacity. Sniffs were repeated approximately once per minute. Pdi was derived electronically from the equation Pdi = gastric pressure $-$ Pes, and was continuously plotted on chart paper. Patients were instructed to watch the pen deflections caused by their efforts and attempt to maximize the pen deflections. Sniffs were repeated until patients had at least three reproducible efforts. The highest Pdi achieved was recorded as the patient's Pdi-sniff. Arterial blood gas measurements were performed with a blood analyzer (Radiometer ABL-520; Radiometer Medical; Brønshøj, Denmark). Arterial puncture of the radial artery or brachial artery was performed, and the sample was processed immediately. Height, weight, and age were measured by pulmonary function technicians at the time of testing. The ΔFVC was calculated by subtracting the supine FVC (percent predicted) from the upright FCV (percent predicted).

Physical Examination Findings

Abdominal paradox and use of accessory muscles were determined by a senior pulmonary physician (C.W.). The presence of accessory muscle use was defined as visible contractions of the sternocleidomastoid or scalene muscles in the supine position. Abdominal paradox was defined by the presence of inward movement of the abdomen during inspiration in the supine position. Examination for these findings was performed prior to measurement of Pdi-sniff.

Statistical Analysis

Potential predictor variables included age, height, weight, upright FVC (liters), FVC (percent predicted), upright FEV_1

(liters), upright FEV_1 (percent predicted), supine FVC (liters), supine FVC (percent predicted), supine FEV_1 (liters), supine FEV_1 (percent predicted), MIP, MEP, $PaCO_2$, and ΔFVC. Bivariate analysis consisted of constructing scatterplots of each potential predictor variable vs Pdi-sniff (centimeters of water). These were visually inspected for the presence of linear relationships. Simple linear regressions were then performed for each predictor variable with Pdi-sniff as the dependant variable.

Analysis of variance was used to compare the relationship between dichotomous predictors (abdominal paradox, accessory muscle use, and gender) and Pdi-sniff. All variables that were significantly associated with Pdi-sniff in simple linear regression ($p < 0.05$) were considered for inclusion in a multivariate model to predict Pdi-sniff. To limit collinearity in the models, the independent predictor variables were analyzed using Pearson correlation coefficients. The predictor variables were included in the models if the correlation coefficient was < 0.6. Another model included gender, height, and the predictor from simple linear regression with the highest correlation coefficient. Sensitivity analysis was carried out using Pdi-sniff < 70 as the cutoff for normal diaphragmatic strength.[7] Statistical significance was set at $p < 0.05$. Where applicable, results are presented as mean ± SD. Analyses were carried out using statistical software (Stata 6.0; Stata Corporation; College Station, TX).

Results

During the study period, 73 patients with ALS were referred for evaluation, of whom 25 patients (34.2%) had sufficient pulmonary function data for analysis. The patients who were not included in these analyses were similar to the reported patients with respect to age, gender, disease duration, mean FVC, and area of disease onset. The patient characteristics appear in Table 1. The mean age was 61.4 years, and the majority of patients were male. The mean body mass index (BMI) was 24.5 ± 4.1 kg/m^2. At the time of pulmonary testing, the duration of ALS symptoms ranged from < 1 year to > 13 years. By the time of pulmonary evaluation, virtually all patients had some degree of bulbar muscle involvement. Fourteen patients had never smoked, and 4 patients had a > 10 pack-year history of tobacco use. The mean upright FVC was only 62.0% predicted, the mean MIP was -39.1 cm H_2O (normal is < -70 cm H_2O),[7,17,18] the mean Pdi-sniff was 33.6 cm H_2O, and the $PaCO_2$ was elevated, on average, to 48.6 mm Hg. The mean FEV_1/FVC was 82.0 ± 6.4; two patients had evidence of airways obstruction. Only 2 of the 25 patients tested had normal Pdi (> 70 cm H_2O).[7]

Table 2 contains the results of simple and multiple linear regression. Upright FVC, supine FVC, and MEP were significantly correlated with Pdi-sniff; however, MIP and $PaCO_2$ were not. There was one patient who had a normal MIP (-84.3 cm H_2O) but a very low Pdi-sniff (12 cm H_2O). This may represent a case in which the subject had excellent accessory muscle strength but a weak diaphragm. When this individual was omitted from analysis, MIP was significantly associated with Pdi-sniff. Supine FVC as a percent of the predicted value was more closely correlated with Pdi-sniff than any other predictor

Table 1—*Patient Characteristics

Characteristics (n = 25)	Data
Age, yr†	61.4 ± 9.8
Range	34.1–76.8
Male gender, %	64.0
BMI, kg/m^2	24.5 ± 4.1
Range	18.1–34.1
Smoking history, pack-yr	10.3 ± 23.4
Range	0–80
Duration of disease, yr‡	2.8 ± 2.0
Range	0.4–13.1
Area of onset, No. (%)	
Limb	22 (91.7)
Bulbar	2 (8.3)
Bulbar involvement, No. (%)	19 (95.0)
Upright FVC (n = 25), L	2.2 ± 0.9
Upright FVC, % predicted	62.0 ± 20.7
Supine FVC (n = 23), L	2.0 ± 0.9
Supine FVC, % predicted	51.8 ± 22.0
ΔFVC (n = 23), %§	11.1 ± 9.0
Upright FEV_1, L	1.9 ± 0.8
Upright FEV_1, % predicted	63.9 ± 20.2
FEV_1/FVC	82.0 ± 6.4
MIP (n = 19), cm H_2O	− 39.1 ± 19.8
MEP, cm H_2O	55.0 ± 33.2
Pdi-sniff (n = 25), cm H_2O	33.6 ± 21.6
$PaCO_2$ (n = 18), mm Hg	48.6 ± 12.7

*Data are presented as mean ± SD unless otherwise indicated.
†Age at the time of pulmonary testing.
‡Duration of disease from onset of symptoms.
§Change from upright FVC (% predicted) to supine FVC (% predicted).

Table 2—*Results of Linear Regression to Predict Pdi-sniff

Variables	Coefficient	p Value	R^2
Supine FVC, % predicted	0.91	< 0.001	0.76
Upright FVC, % predicted	0.71	< 0.001	0.48
Supine FVC, L	13.55	< 0.02	0.36
Upright FVC, L	9.86	< 0.05	0.19
Supine FEV_1S†	0.83	< 0.07	0.69
Upright FEV_1†	0.71	< 0.09	0.44
MEP, cm H_2O	0.42	< 0.05	0.30
MIP, cm H_2O	− 0.45	0.30	0.17
With outlier excluded	− 0.91	< 0.001	0.54
ΔFVC	− 0.47	0.40	0.04
$PaCO_2$, mm Hg	− 0.37	0.50	0.05
Supine FVC (% predicted) and MIP		< 0.001	0.93
Supine FVC (% predicted) and MEP		< 0.001	0.91

*MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure; ΔFVC = difference from upright FVC to supine. p Value reflects F-test for probability of no relationship between predictors and Pdi-sniff. R^2 is the coefficient of determination.
†Percent predicted.

variable, and explained 76% of the variance among the observed values of Pdi-sniff. Supine FVC can be used to predict Pdi-sniff using the following regression equation: Pdi-sniff = − 10.52 + (0.91 × supine FVC percent predicted). Upright FVC was significantly associated with Pdi-sniff but was not as highly correlated with Pdi-sniff as supine FVC (percent predicted). Supine and upright FEV_1 (percent predicted) had similar relationships to Pdi-sniff as FVC but were not as highly correlated. The graphical relationships of supine and upright FVC (percent predicted) with Pdi-sniff are shown in Figures 1, 2. Figure 1 shows a clear positive linear relationship between supine FVC and Pdi-sniff. There is evidence of a positive linear relationship between upright FVC and Pdi-sniff as well (Fig 2), but the relationship appears weaker.

Use of accessory muscles and presence of abdominal paradox were both significantly associated with a lower Pdi-sniff ($p < 0.02$ and $p < 0.03$, respectively). The mean ± SD Pdi-sniff for patients with use of accessory muscle use was 25.9 ± 15.5 cm H_2O, and it was 64 ± 17.7 cm H_2O when accessory muscle use was not present. In patients with abdominal paradox, the mean Pdi-sniff was 21.7 ± 18.4 cm H_2O, while in patients without evidence of abdominal paradox it was 41.2 ± 21.8 cm H_2O. These relationships are shown graphically in Figures 3, 4.

In order to examine the clinical utility of the various diagnostic tests, we calculated sensitivity and specificity. We have presented the results using common clinical cutpoints as well as cutpoints that provide better sensitivity or specificity based on our data. These data are shown in Table 3. These analyses are somewhat limited by the small number of patients with normal Pdi-sniff (> 70 cm H_2O). Supine FVC < 75% predicted was 100% sensitive and 100% specific. MIP (91%), accessory muscle use (84%), and upright FVC (83%) had high sensitivity while maintaining specificity (100%).

To determine if use of data from multiple tests performed better than individual tests, we conducted multivariate analyses using multiple linear regression. A model containing supine FVC (percent predicted) and MEP, (the most predictive single test and the only other significant predictor that was not highly correlated with FVC) was better than supine FVC alone ($p < 0.001$, $R^2 = 0.91$; Table 2). Though MIP was not significantly associated with Pdi-sniff, it is a commonly used measure of inspiratory muscle strength and we therefore examined its contribution to a model containing supine FVC (percent predicted). This model is an excellent predictor of Pdi-sniff ($p < 0.001$, $R^2 = 0.93$). The regression equation to predict Pdi-sniff from this model is as follows: Pdi-sniff = − 3.22 + (1.03 ×

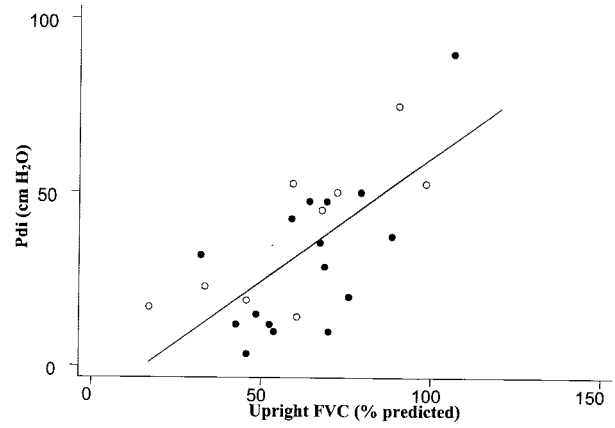

FIGURE 2. Graph of upright FVC (percent predicted) vs Pdi-sniff with regression line. $R^2 = 0.48$; $p < 0.001$; solid circles represent male subjects.

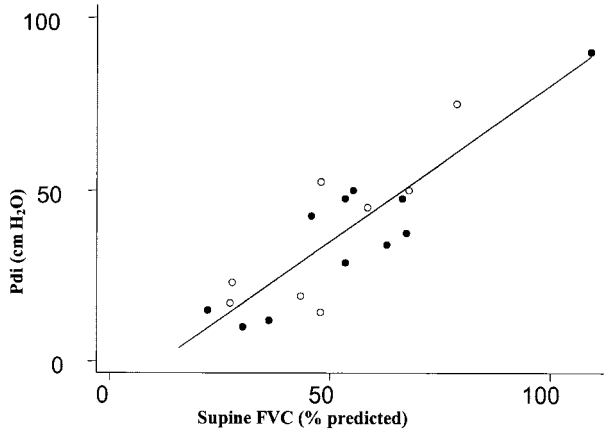

FIGURE 1. Graph of supine FVC (percent predicted) vs Pdi-sniff with regression line drawn. $R^2 = 0.76$; $p < 0.001$; solid circles represent male subjects.

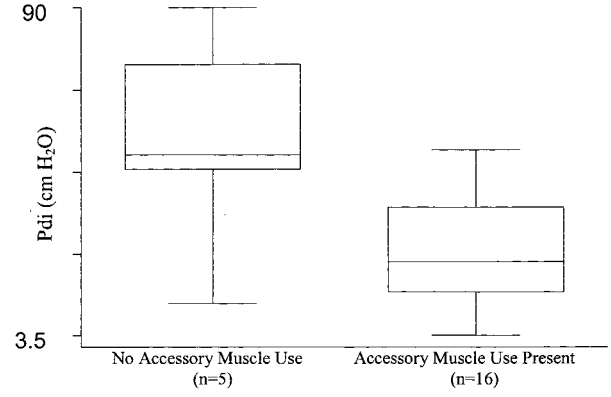

FIGURE 3. Box plot of Pdi-sniff vs accessory muscle use. Pdi-sniff was significantly lower in patients with accessory muscle use ($p < 0.02$). Middle line represents median Pdi-sniff, and boundaries of box represent the 25th and 75th percentile limits.

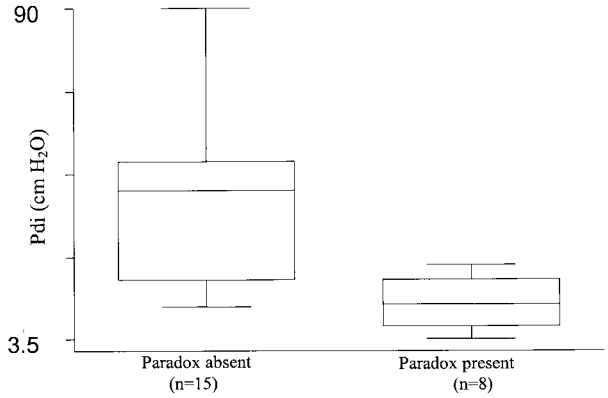

FIGURE 4. Box plot of Pdi-sniff vs abdominal paradox. Pdi-sniff is significantly higher in patients without abdominal paradox ($p < 0.03$). Middle line represents median Pdi, and boundaries of box represent the 25th and 75th percentile limits.

supine FVC) + (0.23 × MIP). Because predicted FVC incorporates gender, height, and age[14] from a different population than ours, we assessed a model containing supine FVC in liters with gender, height, and age. This model was essentially identical to supine FVC as percent predicted ($p < 0.001$, $R^2 = 0.75$). A model containing supine FVC (liters), MIP, age, height, and gender predicted 98% of the variance in Pdi-sniff.

DISCUSSION

This study shows that supine FVC is an accurate, noninvasive means to estimate Pdi-sniff. Combining two tests, supine FVC and MIP, is better than supine FVC alone. Our data show that supine FVC at < 75% predicted is very sensitive and specific for identifying diaphragmatic weakness, and we have also included a regression equation that can be used to estimate Pdi-sniff. The results of this study may allow for the substitution of a noninvasive measure of diaphragmatic strength for an invasive test in many patients. Further study is needed to determine if supine FVC reflects changes in diaphragmatic strength over time.

Table 3—*Sensitivity and Specificity of Tests to Predict Pdi-sniff < 70 cm H_2O

Diagnostic Tests	Sensitivity	Specificity	PPV	NPV
Supine FVC, < 75% predicted	1.0	1.0	1.0	1.0
Supine FVC, < 50% predicted	0.53	1.0	1.0	0.18
Upright FVC, < 75% predicted	0.83	1.0	1.0	0.33
Upright FVC, < 50% predicted	0.30	1.0	1.0	0.22
MIP, <− 80 cm H_2O	0.91	1.0	1.0	0.5
$PaCO_2$, > 45 mm Hg	0.33	1.0	1.0	0.14
Accessory muscle use	0.84	1.0	1.0	0.40
Abdominal paradox	0.38	1.0	1.0	0.13

*PPV = positive predictive value; NPV = negative predictive value.

An encouraging finding of our study was the high sensitivity and specificity of accessory muscle use for detecting diaphragmatic weakness. Therefore, the lack of accessory muscle use can exclude diaphragmatic weakness in many patients. In contrast, upright FVC and $PaCO_2$ at standard cutoffs were rather insensitive tests of diaphragmatic weakness. Hence, reliance on hypercapnia or a severe reduction in FVC to diagnose diaphragmatic weakness will overlook many patients with weakened diaphragms. Accessory muscle use was only assessed by one clinician. This is a subjective measure, and care should be taken before generalizing these finding to less experienced clinicians.

It is well established in healthy volunteers that lung volume and vital capacity decrease after moving from the upright to supine position.[7,19–23] This phenomenon is thought to be due to shifting of blood to the pulmonary vasculature, changes in the position of the diaphragm, and the weight of the abdominal viscera pressing against the diaphragm. In healthy adults, the FVC falls by approximately 7.5 ± 5.7%.[17] This change is exaggerated in many patients with severe diaphragmatic weakness[22]; though it has not been well evaluated in ALS patients, the assessment of ΔFVC has been suggested as a screening test for diaphragmatic weakness.[7,22] Interestingly, in our patients, ΔFVC did not correlate significantly with Pdi-sniff. Of 19 patients who had ΔFVC calculated, 11 patients had large decreases (> 10 percentage points) from upright to supine, but 5 patients had smaller decreases and 3 patients actually had increases in FVC when lying supine. One patient's predicted FVC increased by 10.4 percentage points when lying supine. This was a young woman with definite diaphragmatic weakness (Pdi-sniff = 17 cm H_2O) and dyspnea at rest who had no abdominal paradox and felt more comfortable lying supine.

It is not clear why ΔFVC did not correlate with Pdi-sniff in our patients. If FVC decreases in the supine position due to pressure of abdominal viscera against the diaphragm when lying supine, this effect would be expected to be larger in obese subjects. While the effect of obesity on ΔFVC is not well established, obese patients do have a larger supine decrement in MEP than nonobese subjects.[24] Our patients frequently had recent weight loss and relatively low BMIs, which may have accounted for some of the variability seen. Since ALS patients develop diffuse muscle weakness, their respiratory mechanics may be similar to patients with cervical spinal cord lesions. One component of the inspiratory action of the diaphragm relies on rib cage appositional forces

that increase the diameter of the lower rib cage. These appositional forces are determined in part by the area of apposition between the costal diaphragm and the lower rib cage and by resistance provided by the abdominal contents.[25] If the compliance of the abdominal wall is increased, the abdominal pressure generated during inspiration will be less and the diaphragm will be less effective. If patients lack abdominal muscle tone, abdominal pressure will not increase with inspiration and appositional forces will be decreased.[26] However, the compliance of the abdominal wall is believed to increase when assuming a supine posture. This should result in worsened diaphragmatic function when lying supine. Strohl and colleagues[27] demonstrated that a subset of quadriplegic patients had decrements in tidal volume when seated compared to supine. This was believed to be due to shortening of the diaphragm to a less effective position when seated.[27] Radiologic studies[26] have confirmed that quadriplegic patients have increased zones of diaphragmatic apposition when lying supine. ALS patients with abdominal and thoracic muscle weakness may exhibit similar physiology to quadriplegic patients and behave less like patients with diaphragmatic paralysis, and therefore may have improvement in vital capacity when lying supine.

This study is unique in that we compared several noninvasive measures of respiratory function, including a less common measure, supine FVC, to predict diaphragmatic strength (Pdi-sniff) in a group of patients with a well-characterized neuromuscular disease. The demographic characteristics of our sample are similar to other groups of ALS patients,[28] but the pulmonary function test results suggest that this group was referred for evaluation only after they had significant respiratory muscle weakness. Though the total number of patients is comparable to other studies of pulmonary function in ALS,[5,29,30,31] we were somewhat limited by the small number of patients with normal respiratory muscle strength. Furthermore, not all patients completed all of the pulmonary tests. Therefore, a relatively small number of patients had $Paco_2$ and mouth pressures measured. Two of our patients had obstructive lung disease based on pulmonary function testing. Though the results in these two patients were consistent with the patients without obstructive defects, it is unclear whether our findings can be generally applied to ALS patients who also have concomitant lung diseases. Additionally, although the assessment of accessory muscle use and abdominal paradox was made prior to the measurement of Pdi-sniff, it was not always made in the absence of other pulmonary function data. Thus, observer bias may explain the strong relationship between clinical observation and pulmonary function testing.

This study demonstrated that supine FVC is an excellent measure of diaphragmatic strength in patients with ALS. This test may serve as a diaphragmatic "stress test," in that upright FVC may not reveal abnormalities that otherwise become noticeable in the supine position. It is apparent that the diaphragm becomes weak well before the upright FVC is reduced but using the supine FVC $< 75\%$ predicted as a cutoff is a highly sensitive and specific measure of diaphragmatic weakness. Longitudinal studies need to be performed to determine whether supine FVC is a better predictor of future outcomes, including respiratory failure and death, than measures currently in use. It is not known whether early detection of respiratory muscle weakness and intervention leads to improved outcomes in ALS but it will allow interventions to be developed that target mild respiratory impairment.

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