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RESEARCH ARTICLE

Correlation between Forced Vital Capacity and Slow Vital Capacity for the assessment of respiratory involvement in Amyotrophic Lateral Sclerosis: a prospective study

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Abstract

Introduction: Slow vital capacity (SVC) and forced vital capacity (FVC) are the most frequent used tests evaluating respiratory function in amyotrophic lateral sclerosis (ALS). No previous study has determined their interchangeability. *Objective*: To evaluate SVC-FVC correlation in ALS. *Methods*: Consecutive definite/probable ALS and primary lateral sclerosis (PLS) patients (2000-2014) in whom respiratory tests were performed at baseline/4-6months later were included. All were evaluated with revised ALS functional rating scale, the ALSFRS respiratory (R-subscore) and bulbar subscores, SVC, FVC, maximal inspiratory (MIP) and expiratory (MEP) pressures. SVC-FVC correlation was analysed by Pearson product-moment correlation test. Paired *t*-test compared baseline/follow-up values. Multilinear regression analysis modelled the relationship between tested variables. *Results*: We included 592 ALS (332 men, mean onset age 62.6 ± 11.8 years, mean disease duration 15.4 ± 15 months) and 19 PLS (11 men, median age 54 years, median disease duration 5.5 years) patients. SVC and FVC predicted values decreased 2.15%/month and 2.08%/month, respectively. FVC and SVC were strongly correlated. Both were strongly correlated with MIP and MEP and moderately correlated with R-subscore for the all population and spinal-onset patients, but weakly correlated for bulbar-onset patients. *Conclusions*: FVC and SVC were strongly correlated and declined similarly. This correlation was preserved in bulbar-onset ALS and in spastic PLS patients.

Key words: *Amyotrophic lateral sclerosis*, *forced vital capacity*, *slow vital capacity*, *functional rating scale*, *maximal respiratory pressures*

INTRODUCTION

Respiratory insufficiency (RI) and other respiratory complications resulting from weakness of the respiratory muscles are the main cause of death in Amyotrophic Lateral Sclerosis (ALS) (1). Although usually a late event during the course of the disease, RI can be the presenting feature (2). As the respiratory muscle weakness emerges, patients with ALS complain of dyspnoea on exertion, orthopnea, abnormal sleep, morning headaches, daytime sleepiness, cough impairment and respiratory infections (1).

Several different and complementary tests assessing respiratory function in ALS have been studied. Forced vital capacity (FVC), slow vital capacity (SVC; also called vital capacity in some studies), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and sniff nasal inspiratory pressure (SNIP) are non-invasive tests frequently used in clinical practice. FVC predicts prognosis in ALS (3,4) and can be more sensitive in detecting diaphragmatic weakness when performed in the supine position (5). FVC is predictive of hypercapnia (6) and it is generally used to monitor ALS patients (3,7,8). Values of arterial blood gases tend to be normal until FVC measurements are very low (3,9). MIP is more sensitive than FVC in detecting hypoventilation (10) but it is difficult to perform in patients with marked orofacial paresis (11). In addition, it is not a good test to follow patients for long periods as it has a marked early decline (floor effect). SNIP and nocturnal pulse oximetry are sensitive tools especially suited for ALS patients with orofacial paresis and both predict survival (12–14). In addition, SNIP is predictive of

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hypoventilation in patients with spinal-onset ALS (15). Diaphragmatic motor response by percutaneous electrical phrenic nerve stimulation in the neck to elicit motor responses is a non-volitional test that predicts hypoventilation and survival in ALS (16–18). The amplitude of the motor response shows significant changes over short follow-up periods (3–6 months), suggesting its utility in clinical trials (16–18). Clinically, the respiratory subscore of the revised ALS functional rating scale (R-subscore) is routinely used worldwide to monitor symptoms of respiratory involvement (19), but gives limited information and can be misleading in some patients (20).

In addition to FVC, SVC has long been used to assess respiratory function in ALS. Both depend on age, gender, height, weight and ethnicity of the individuals (21). There seems to be little or no difference between SVC and FVC in normal subjects (22). However, some studies have found that FVC values are lower than SVC in patients with asthma and chronic obstructive pulmonary disease (COPD) due to airflow limitation, small airway collapse and gas trapping (22–24). In asthma and in bronchiolitis obliterans syndrome after lung transplantation, the difference increases with obstruction severity and can be an indicator of air trapping (22,25,26). It has been shown that not only the difference between SVC and FVC but also the FVC/SVC ratio is an indicator of airflow obstruction and exercise tolerance (26,27).

In ALS there are no studies comparing SVC and FVC. This subject is particularly relevant for clinical management of ALS patients and clinical trials. FVC can be technically more difficult to perform by ALS patients with orofacial paresis as a higher volume of air can be lost between the mouthpiece and the weak lips. Consequently, underestimated values can lead to early introduction of non-invasive ventilation (NIV), thus excluding otherwise eligible subjects for clinical trials.Furthermore, it is not known whether spasticity can have a preferential impact in FVC, as a rapid expiratory movement. Finally, it is not possible to exclude differences between SVC and FVC in ALS due to air trapping in patients with severe expiratory muscle involvement and atelectasis.

In different ALS centres, respiratory assessment is done using either SVC or FVC, but not both. This practice is mirrored in clinical trials, in which one single measurement is used as outcome, although we do not know if they give similar information.

With the present study we aim to investigate the correlation between SVC and FVC in a longitudinal data set from a large population of ALS patients. We complement this evaluation with the results from clinical evaluation and other respiratory tests. We addressed bulbar-onset and primary lateral sclerosis (PLS) patients to observe the influence of facial weakness and spasticity on the results.

PATIENTS AND METHODS

Study population

Inclusion criteria

We included consecutive patients with ALS (with definitive or probable disease accordingly to the revised El Escorial criteria) and PLS followed in the ALS Clinic of the Department of Neurosciences, Hospital de Santa Maria-CHLN, in Lisbon, from January 2000 to December 2014. PLS diagnosis was established using the Pringle et al. criteria (28), with 4 or more years of clinical progression without lower motor neuron dysfunction, as suggested elsewhere (29).

Exclusion criteria

Patients with other medical conditions, in particular heart failure, anaemia, history of thoracic surgery, asthma and COPD were excluded. In addition, patients with clinical signs of dementia or unable to cooperate with the respiratory tests were not recruited.

Investigations

All investigations were performed within one month after the first clinical observation (baseline) and 4 and 6 months later for ALS and PLS patients, respectively.

a) Clinical evaluation

All patients were evaluated with ALS functional rating scale (ALSFRS), revised ALSFRS (ALSFRS-R), bulbar subscore of ALSFRS-R (B-subscore, including the 3 first questions of ALSFRS-R, scored 0-12); respiratory subscore (R-subscore, including the last 3 questions of ALSFRS-R, scored 0-12), upper limb subscore (UL–score, including questions 4,5 and 6 of ALSFRS-R, scored 0-12) and lower limb subscore (LL-subscore, including questions 7, 8 and 9 of ALSFRS-R, scored 0-12).

b) Respiratory function tests

For each patient the respiratory function tests were performed with the same devices and by the same technicians, always using nose clips for nose occlusion and according to ATS/ERS guidelines (30):

b1) SVC and FVC. SVC and FVC were determined with the patients in the sitting position, by using a computer-based USB spirometer (microQuark®, Cosmed®) or standard Jäger equipments (two Jäger® Masterlab®, and one Jäger® Masterscreen®, Erich Jäger, GmbH, Würzburg, Germany). All measurements were performed by one of the authors (SP), using microQuark®, Cosmed®, and the same technician for Jäger® equipments. The best of three satisfactory and consistent expiratory manoeuvres,

each obtained after a maximal inspiratory effort, was used to determine the values of FVC and SVC. Predicted values (%) were used for statistical analysis (31).

b2) MIP and MEP. MIP and MEP were measured in the sitting position with a MicroRPM® device (CareFusion®) by one of the authors (SP) and by the same technician for the Jäger® equipments. The best result from three consistent measurements of MIP and MEP at the mouth against occluded inspiratory and expiratory airways, respectively, was used for statistical analyses, using its percentage of predicted values (%).

Statistical analysis

The primary endpoint of this study was to investigate the correlation between SVC and FVC in ALS in a longitudinal data set from a large population of patients. Secondary endpoints included evaluation of possible differences in sensitivity between FVC and SVC as well as correlation of SVC and FVC values with other clinical (ALSFRS-R, R-subscore) and maximal pressures (MIP and MEP) evaluations. The Pearson moment correlation test was used to evaluate the correlation between SVC and FVC, and correlations between these measurements and R-subscore, UL-subscore, LL-subscore, MIP and MEP (for the total population and for subgroups according to type of ALS onset). Paired t-test analyses were used to compare measurements at baseline and 4 months after, in the total population and in the spinal and bulbar subgroups. The same comparisons between baseline versus 4-month were done in the groups of patients with (R-subscore <11) and without (R-subscore ≥ 11) significant respiratory symptoms. Multilinear regression analysis (backward method) was applied to evaluate the relationship of FVC/SVC with clinical features – gender, age at onset, onset form, disease duration at study entry, ALSFRS, bulbar-subscore, UL-subscore, LL-subscore, R-subscore, MIP and MEP.

Local ethics' committee

The protocol for respiratory evaluations was approved by the Centro Hospitalar Lisboa Norte-Faculdade de Medicina Joint Ethics' Committee.

RESULTS

We included 592 ALS patients (332 men; mean onset age 62.6 ± 11.8 years; mean disease duration 15.4 ± 15 months). Onset form was spinal in 382 patients, bulbar in 184, respiratory in 10 and predominant axial muscle weakness or generalised disease in 16. All patients repeated the respiratory tests at baseline and at 4 months. Values of the functional scores and percentage of predicted values (%) of the respiratory tests are summarised in Table 1. As the number of patients with respiratory and axial/generalised onset was small, no specific statistical analyses was considered for these groups. The additional group of 19 patients with PLS had a median age at disease onset of 54 years (range 47-71 years) and median disease duration of 5.5 years (range 5-7 years). Eight of these patients were women.

Table 1. Values of the functional scores and percentage of predicted values (%) of the respiratory tests performed at study entry and 4 months after.

	Baseline	4 months after	*p*
ALSFRS	32.4 ± 5.2	28.85 ± 7.1	<0.001
ALSFRS-R	40.2 ± 5.4	36.6 ± 7.5	<0.001
B-subscore	10.2 ± 2.3	9.5 ± 2.9	<0.001
UL-subscore	9.43 ± 2.6	8.2 ± 3.4	<0.001
LL-subscore	9.15 ± 2.7	8 ± 3.2	<0.001
R-subscore	11.4 ± 1.1	10.8 ± 1.7	<0.001
SVC (% predicted)	93.3 ± 19.6	85 ± 24.8	<0.001
FVC (% predicted)	94.0 ± 19.8	85.4 ± 25.6	<0.001
MIP (% predicted)	58.9 ± 26.7	53.1 ± 28.5	<0.001
MEP (% predicted)	74.6 ± 29.1	64.2 ± 33.2	<0.001

ALSFRS: ALS functional rating scale; ALSFRS-R: Revised ALS functional rating scale; B-subscore: Bulbar subscore of ALSFRS-R; FVC: Forced vital capacity; LL-subscore: Lower limb subscore of ALSFRS-R; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; R-subscore: Respiratory subscore of ALSFRS-R; SVC: Slow vital capacity; UL-subscore: Upper limb subscore of ALSFRS-R.

For the total ALS population and for spinal and bulbar onset patients there was a significant decrease of all variables between the two evaluation times ($p < 0.001$). In the total population, percentage of predicted values of FVC and SVC had a mean decrease of 2.15%/month and 2.08%/month, respectively. In the subgroups of patients with significant respiratory symptoms (R-subscore <11), all measurements decreased significantly, except for MIP in patients with R-subscore <11 ($p = 0.082$).

FVC and SVC in ALS patients were strongly correlated both at baseline ($r^2 = 0.98$ for the total population and spinal-onset patients, and $r^2 = 0.96$ for bulbar-onset patients, $p < 0.001$) and 4 months after ($r^2 = 0.98$ for the total population and spinal-onset patients, and $r^2 = 0.94$ for bulbar-onset patients, $p < 0.001$) – Figure 1. FVC and SVC were also strongly correlated with MIP and MEP and moderately correlated with R-subscore in the total population and spinal-onset patients at both evaluations. For bulbar patients, although correlations were statistically significant, they tended to be weaker between FVC and SVC with R-subscore (Table 2). In the subgroups of ALS patients with and without respiratory involvement, there was a strong correlation between FVC and SVC in both evaluation periods ($r = 0.974$ and 0.975 for patients without respiratory involvement respectively for

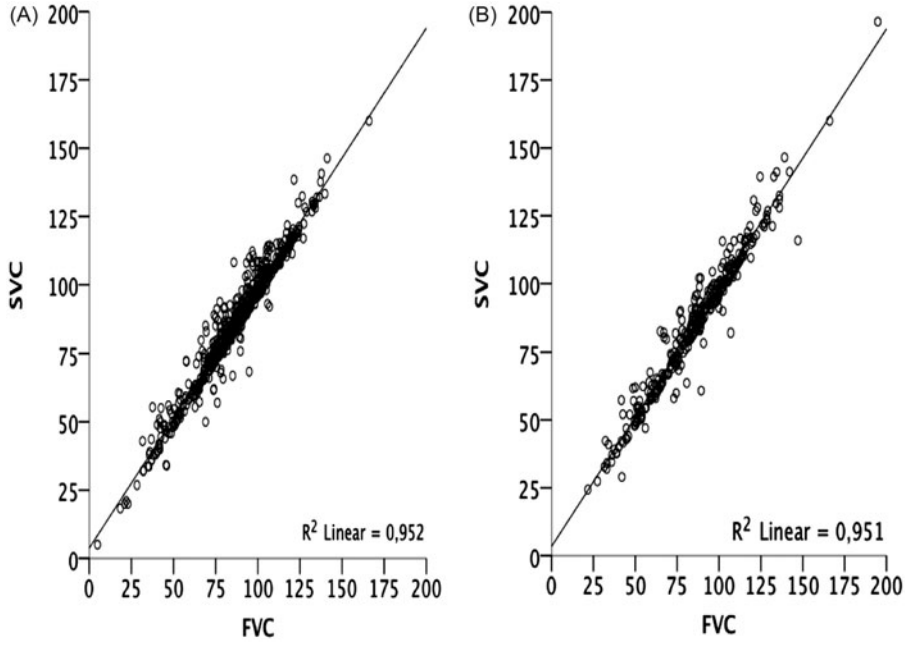

Figure 1. SVC-FVC correlation at: A. Baseline; B. Four months after.

Table 2. Correlation analyses (*r* values are shown).

	ALSFRS-R	R-subscore	SVC	FVC	MIP	MEP
All population						
Baseline						
SVC	0.427**	0.385**	1	0.976**	0.508**	0.590**
FVC	0.424**	0.366**	0.976**	1	0.520**	0.596**
4mo after						
SVC	0.487**	0.303**	1	0.975**	0.565**	0.634**
FVC	0.478**	0.305**	0.975**	1	0.546**	0.636**
Spinal onset patients						
Baseline						
SVC	0.471**	0.440**	1	0.980**	0.510**	0.603**
FVC	0.459**	0.430**	0.980**	1	0.510**	0.600**
4mo after						
SVC	0.537**	0.318**	1	0.983**	0.586**	0.669**
FVC	0.532**	0.312**	0.983**	1	0.563**	0.681**
Bulbar onset patients						
Baseline						
SVC	0.432**	0.302**	1	0.962**	0.427**	0.474**
FVC	0.445**	0.275**	0.962**	1	0.451**	0.484**
4 mo after						
SVC	0.409**	0.246*	1	0.943**	0.381**	0.438**
FVC	0.406**	0.243*	0.943**	1	0.378**	0.413**

ALSFRS-R: Revised ALS functional rating scale; FVC: Forced vital capacity; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; mo: Months; R-subscore: Respiratory subscore of ALSFRS-R; SVC: Slow vital capacity.
**Significant for $p<0.001$.
*Significant for $p<0.05$.

baseline and after 4 months; $r=0.966$ and $r=0.963$ in patients with respiratory involvement respectively for baseline and after 4 months, $p<0.001$). In the subgroup of patients with R-subscore <11 we found a lower correlation between SVC and FVC and MIP ($r=0.585$ and 0.572 at baseline and $r=0.577$ and 0.579 after 4 months, respectively).

At baseline, for the total ALS population, percentage of predicted value for FVC and SVC were associated with gender (higher in men, $p<0.001$); ALSFRS ($p<0.001$), bulbar-subscore ($p=0.004$ for FVC and $p=0.025$ for SVC), UL–subscore ($p<0.001$ for FVC and $p=0.001$ for SVC), LL-subscore ($p=0.007$ for FVC and $p=0.028$ for SVC), MIP ($p<0.001$) and MEP ($p<0.001$). After 4 months, for the total population, FVC and SVC were associated with ($p=0.004$ for FVC and $p=0.001$ for SVC);

ALSFRS ($p<0.001$), MIP ($p<0.001$) and MEP ($p<0.001$).

In the 19 PLS patients FVC and SVC were strongly correlated both at baseline and 6 months after ($r=0.993$ and $r=0.997$, respectively, $p<0.001$).

DISCUSSION

Respiratory function in ALS patients should be monitored to detect signs of respiratory impairment that, in association to clinical symptoms, support the indication for non-invasive ventilation (32,33). Moreover, as hypoventilation is predictive of survival in ALS (3,4), it is necessary to include respiratory evaluation in the design of clinical trials. NIV is associated with increased survival and quality of life in ALS, at least for those patients without major bulbar involvement (34,35).

FVC has been extensively used in ALS, in particular in clinical trials. SVC is a less demanding test for patients. It is also frequently used in ALS in trials and to monitor disease progression. Both depend on patient's cooperation and could be underestimated in patients with marked facial paresis. SNIP has been proposed as an option because is not as affected by lip weakness. Nonetheless, the learning effect impact is important for SNIP determination, which has potential major implications in patients' follow-up (36).

The hypothesis in this study was that values of FVC and SVC are statistically similar in ALS. However, as forced exhalation is a necessary condition for FVC determination, fatigue, lower airflow patency and expiratory muscle weakness could have a higher impact in FVC than in SVC. To our knowledge no study has explored possible differences between FVC and SVC in ALS patients.

In this study, we used the percentage of the predicted value of the respiratory tests, as usually applied to show respiratory test results and recommended for evaluating respiratory function (37). Our results show that FVC and SVC predicted values are strongly correlated and decline similarly in patients with ALS and PLS, including patients with bulbar-onset ALS. Furthermore, both FVC and SVC are strongly correlated with MIP and MEP, and moderately correlated with clinical scores. As derived from a multiregression model, both FVC and SVC are influenced by gender, MIP and MEP at the two evaluation timings, and associated with the ALSFRS. However, FVC and SVC are not associated with on R–subscore, which indicates that the respiratory subscale of the ALSFRS is less sensitive to the decline in respiratory status than are direct objective measurements. In fact, Cedarbaum *et al.* found no correlation between FVC and the respiratory question of the ALSFRS (38).

In patients with relevant symptoms of respiratory distress (R–subscore <11) the correlation between FVC and SVC with MIP is weaker, possibly relate to two major factors: MIP floor effect and technical difficulties in recording a reliable MIP value in patients with marked facial paresis or have marked respiratory fatigue. Additionally, a less effective coordination between the respiratory and voluntary upper airways muscles can give a contribution to poor MIP evaluation performance. This poor coordination can explain the weaker correlation between FVC and SCV in bulbar-onset patients, in particular at the second evaluation.

In conclusion, our results show that FVC and SVC provide interchangeable information regarding respiratory function in ALS, but that respiratory symptoms as determined by the ALSFRS are poorly correlated with these measurements.

Declaration of interest

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