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Minerva Medica 2018 December;109(Suppl. 1 to No. 6):11-9
DOI: 10.23736/S0026-4806.18.05920-7

REVIEW

XIII PNEUMOLAB PROCEEDINGS

Respiratory muscle testing in amyotrophic lateral sclerosis: a practical approach

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ABSTRACT

In amyotrophic lateral sclerosis (ALS), respiratory muscle weakness leads to respiratory failure and death. Non-invasive positive pressure ventilation (NIPPV) appears to reduce lung function decline, thus improving survival and quality-of-life of patients affected by the disease. Unfortunately, clinical features and timing to start NIPPV are not well defined. Starting from recent findings, we examine established and novel tests of respiratory muscle function that could help clinicians decide whether and when to start NIPPV in ALS. Non-invasive tests estimate the function of inspiratory, expiratory, and bulbar muscles, whereas clinical examination allows to assess the overall neurologic and respiratory symptoms and general conditions. Most of the studies recommend that together with a thorough clinical evaluation of the patient according to current guidelines, vital capacity, maximal static and sniff nasal inspiratory pressures, maximal static expiratory pressures and peak cough expiratory flow, and nocturnal pulse oximetry be measured. A sound understanding of physiology can guide the physician also through the current armamentarium for additional supportive treatments for ALS, such as symptomatic drugs and new treatments to manage sialorrhea and thickened saliva, cough assistance, air stacking, and physiotherapy. In conclusion, careful clinical and functional evaluation of respiratory function and patient's preference are key determinants to decide "when" and "to whom" respiratory treatments can be provided.

(*Cite this article as:* Sferrazza Papa GF, Pellegrino GM, Shaikh H, Lax A, Lorini L, Corbo M. Respiratory muscle testing in amyotrophic lateral sclerosis: a practical approach. Minerva Med 2018;109(Suppl. 1 to No. 6):11-9. DOI: 10.23736/S0026-4806.18.05920-7)

KEY WORDS: Amyotrophic lateral sclerosis - Respiration disorders - Respiratory muscles - Spirometry.

Respiratory failure due to relentless progression of respiratory muscle weakness is the main cause of death in patients with amyotrophic lateral sclerosis (ALS).[1] The time from ALS diagnosis to death or respiratory muscle paralysis is on average 2-3 years.[2] Although riluzole is a licensed drug for ALS treatment,[3] its effects on survival are modest. Other treatments are urgently required.[4] Respiratory symptoms occur late in the disease and portend decreased survival.[5, 6] In contrast, respiratory function defects occur early in the disease as a result of respiratory muscle weakness (Figure 1) and assist in the decision to start non-invasive positive pressure ventilation (NIPPV). Of clinical relevance, survival in patients under NIPPV has been proven to be signifi-

cantly higher if NIPPV was initiated earlier.[7, 8] In addition, respiratory functional evaluation provides prognostic information and allows for risk-stratification prior to percutaneous endoscopic gastrostomy (PEG) tube placement.[9] Societal recommendations suggest measurements of vital capacity (VC) over time to quantify respiratory muscle weakness in patients with ALS.[9, 10] However, VC has physiological limitations in assessing muscle strength[11-13] and is technically challenging in about 20% of patients mainly because of bulbar dysfunction.[14]

Literature search and aims of this review

English literature was reviewed since the landmark paper of Black *et al.*[15] on maximal static respiratory pressures in generalized neuromuscular disease to date (1971 to 30th November 2017) on PubMed. The following keywords were used: "amyotrophic lateral sclerosis" AND "respiratory muscle tests," "amyotrophic lateral sclerosis" AND "respiratory muscle tests spirometry," "amyotrophic lateral sclerosis" AND "lung volumes," "amyotrophic lateral sclerosis" AND "sniff test" based on title, abstract and MeSH terms. Original studies, editorials, published letters and reviews were included.

Moving forward from recent insights by Polkey *et al.*,[4] we here review the key features of respiratory functional tests in ALS and examine what practical non-invasive approach best assists in the decision to start NIPPV and other supportive treatments for ALS. Finally, unanswered clinical questions concerning the respiratory management of ALS are discussed.

Review findings

Lung function testing in ALS

Combining invasive and non-invasive tests, Polkey *et al.*[4] shed light on the link between respiratory muscle tests and survival in ALS. The gold standard for the assessment of the respiratory muscle strength is the measurement of the force exerted against an occluded valve.[16] In 1969 Black and Hyatt pioneered the non-invasive assessment of the maximal static inspiratory (MIP) and expiratory pressure (MEP).[15, 17] Nowadays, MIP and MEP are non-invasive, readily available, standardized, and economic tests to assess muscle strength.[18] Given the alinear force-length relationship of the respiratory system, MIP decreases earlier than lung volumes with the neuromuscular diseases,[19] reason for which it is considered more sensitive than VC in detecting inspiratory muscle weakness (Figure 1).[20] MIP values less than -70 cmH_20 for women and -80 cmH_20 for men practically tend to exclude clinically relevant inspiratory muscle weakness, while MEP values below 40 cmH_20 are likely to be associated with ineffective cough.[18, 21] However, caution should be used in interpreting MIP and MEP data, as low values may result from a lack of motivation and poor effort.[22] Measurement of the transdiaphragmatic pressure (Pdi)[21, 23-26] is the gold standard to measure the force of the diaphragm. It is the difference between gastric and esophageal pressure and can be assessed during maximal voluntary contraction or upon electrical or magnetic stimulation.[18, 23, 27] Due to its invasive nature and the technical challenges involved in collecting and interpreting the data,[19] this technique is generally limited to reference centers or physiological research.[4, 19, 28]

In clinical practice, assessment of the neurological and respiratory conditions together with lung volumes measurement is of help to raise the suspicion of respiratory muscle weakness, being

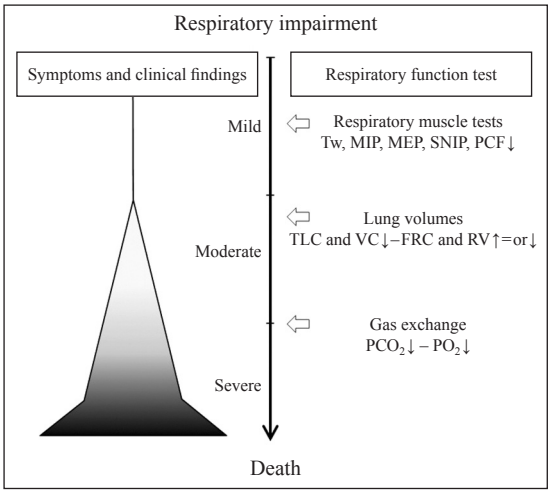

Figure 1.—Respiratory tests sensitivity according to amyotrophic lateral sclerosis disease progression.

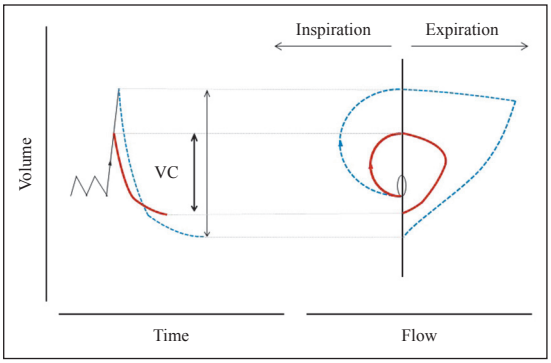

Figure 2.—Schematic representation of lung volume in amyotrophic lateral sclerosis plotted against time (left panel) and flow (right panel) during tidal breathing and forced inspiratory and expiratory manoeuvres. Blue and red lines (in the online version) are predicted and observed tracings, respectively. Dotted and full lines are predicted and observed tracings, respectively. The decrease in vital capacity (VC) may be due to weakness of inspiratory muscles preventing full inflation and/or of the expiratory muscles impairing expiration.

a reduction in vital capacity (VC) a reflection of muscle weakness.[18, 29] VC may be limited by weak inspiratory muscles preventing full inflation and/or weakness of the expiratory muscles impairing expiration, or both (Figure 2).[18] In addition, VC may also be reduced because of a decrease in lung and chest wall compliance as reported in patients affected by neuromuscular diseases.[10, 30, 31] A physiological limitation of spirometry is that a decrease in lung volumes is a relatively late finding compared to the progression of muscle dysfunction.[11] As anticipated above, this is because of the non-linear relationship between respiratory volume and pressure.[12] In mild to moderate muscle weakness, VC is in general less sensitive than maximum respiratory pressures[12] (Figure 1). Moreover, a decrease of VC is non-specific being caused by other potentially associated restrictive lung diseases. Finally, a practical limitation of spirometry in patients with bulbar impairment can be due to mouth leaks and lack of coordinated muscle activity to perform the test.[32]

A different way to assess the strength of the diaphragm is to measure the pressure exerted at the nostril during a sniff, *i.e.*, a short, sharp voluntary inspiratory maneuver.[16] The sniff nasal inspiratory pressure (SNIP) is measured through a pressure transducer placed in a nostril with the other left unoccluded.[22, 33-35] SNIP obviates the need of mouth seal, linearly declines with progression of the disease,[33] and has a high predictive power to predict survival.[4] In general, a SNIP <-50 cmH_20 for women and <-60 cmH_20 for men exclude relevant respiratory muscle weakness.[36] However, SNIP test requires training,[37] and it may have some limitations in patients with bulbar impairment, anatomical abnormalities and nasal congestion.[22, 38]

Cough is a vital reflex that requires the integrity of bulbar, inspiratory and expiratory muscles,[39] with the latter being the dominant determinant of cough. Commercial devices permit to assess peak cough expiratory flow (PCF) as a surrogate for cough effectiveness.[40] In clinical practice, a PCF >160 L/min is sufficient to remove secretions, though values >270 L/min[41-43] may be necessary to clear secretions especially during chest infections.[44]

Polkey *et al.* found that the sniff and twitch transdiaphragmatic pressure had an excellent performance and linearly declined with progression of the disease.[4] Amid non-invasive tests, sniff nasal pressure predicts mortality, while vital capacity remains stable until final stage of the disease. Among the few study limitations, one could argue that exercise (in the early phase) and sleep evaluation could have shown further insight in the progression of the disease and on choice and timing of tests.

Indications for NIPPV

According to the current international guidelines,[9] the decision to start NIPPV in ALS should include a thorough clinical evaluation with special attention to dyspnea and objective tests of respiratory failure. Dyspnea at rest is a criterion to start NIPPV. Yet, as discussed in the following paragraph, how to best measure dyspnea in ALS remains to be elucidated. VC values below 50% of predicted is considered a threshold to start NIPPV. Yet in two studies NIPPV was initiated when VC decreased below 75% or 65% of predicted and this resulted in significantly higher survival.[7, 8] Diffusing capacity of the lung for carbon monoxide (DLCO)[45] may be of help to rule out unexpected associated conditions. Even though MIP and SNIP are the classical markers

of inspiratory muscles strength, a recent study suggested that SNIP is easier to perform and more feasible in advanced disease.[4] In any case, valus of MIP values <60 cmH_20 and/or SNIP <40 cmH_20 suggest to start NIPPV. MEP and PCF are key tests to assess expiratory muscles. A MEP value of <40 or a PCF <270 L/min are shared cut-offs to provide cough assistance.[46, 47] Cough aid may be provided either manually or mechanically according to patient preferences and availability. Oxygen desaturation below 89% for more than 5 consecutive minutes at night is another criterion to start NIPPV[48] and predict survival in ALS.[49-51] In selected cases a full polysomnography may be required. Given that impaired ventilation may worsen during sleep, transcutaneous carbon dioxide and capnography has been used to early detect nocturnal hypoventilation.[52, 53] Yet, this device is still under scientific scrutiny.

Unmet needs in ALS

There are several unmet needs when it comes to assess the early respiratory impairment, monitoring muscle function, and treatments allocation in ALS (Table I).[4, 22, 54-63] ALS presentation with overt respiratory impairment occurs in about 3% of patients and portends reduced survival.[46, 63, 64] Usually, respiratory impairment follows limb or bulbar onset with an asymptomatic involvement of unknown duration (Figure 1). Dyspnea appears to mirror inspiratory muscle weakness and is amid criteria to start NIPPV.[46] Yet, dyspnea at rest is a late finding before occurrence of respiratory failure.[63] Given the contribution of the cortical areas in elaborating the symptom perception,[65] assessing dyspnea is not easy to measure.[66-69] Some patients tend to underestimate dyspnea, partly because of reduction in daily activities or fear, despite marked impairment of spirometry.[70] Different scores have been proposed to best estimate the symptom.[71] Notably, when performed in the supine position, the BORG score quite well correlates with inspiratory muscle weakness.[71] Yet, a prospective comparison of available scores is still lacking. Surely, the onset of dyspnea is ominous and its use as a trigger to respiratory consultation in ALS would result in dangerous delays.

Combining invasive and non-invasive tests, Polkey *et al.* shed light on the link between respiratory muscle tests and survival in ALS. The authors found that the sniff and twitch transdiaphragmatic pressure had an excellent performance and linearly declined with progression of the disease. Amid non-invasive tests, sniff nasal pressure predicts mortality, while VC remains stable until final stage of the disease. Among the few study limitations, one could argue that exercise in the early phase and sleep evaluation could show further insight in the progression of the disease and on choice and timing of tests.[4]

TABLE I.—*Advances and unanswered clinical questions in the respiratory management of amyotrophic lateral sclerosis*.

Advances	Assessment	Spirometry is insensitive to early respiratory muscle weakness and to stratify prognosis[4]
		Primary determinant of ventilatory failure and respiratory symptoms are a result of inspiratory muscle weakness[54]
		Respiratory muscle tests are predictive biomarkers of survival[4, 22, 55]
	Treatment	NIPPV improves quality of life and survival[56, 57]
		Cough assistance is important and devices are effective[58, 59]
		Timely management of dysphagia and secretions are very important to maintain sufficient quality of life[60-62]
Unanswered questions	Assessment	Which is the most accurate score to measure dyspnea?
		What strategies of respiratory muscle testing are more cost-effective in clinical practice?
		How to optimize the assessment in bulbar disease?
		Is diaphragmatic ultrasound accurate in detecting diaphragmatic weakness?
	Treatment	Timing for supportive treatment
		Role for NIPPV in bulbar disease
		Role and intensity of exercise and rehabilitation
		How can we improve patients' survival and QoL without invasive ventilation?
		Role of tele-monitoring in ALS

ALS: amyotrophic lateral sclerosis; NIPPV: non-invasive positive pressure ventilation; QoL: quality of life.

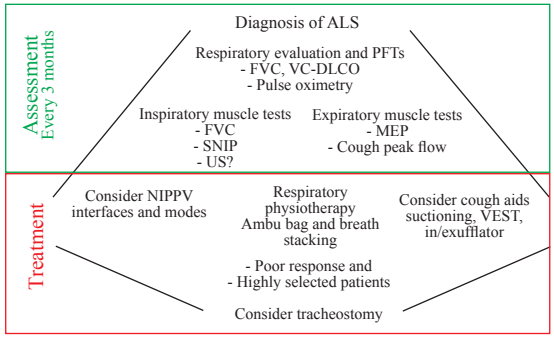

Figure 3.—A non-invasive approach to respiratory muscle testing in amyotrophic lateral sclerosis.

In bulbar impairment both the lung function assessment and supportive treatment (*e.g.* NIPPV) are challenging as frequently biased by leaks resulting from a lack of mouth seal.[56] Specific studies are required to shed light on how to best measure VC in the patients with bulbar impairment.

Several supportive therapies are available for patients with ALS (Figure 3). In addition to NIPPV,[14, 56, 72-76] symptomatic drugs and specific treatments to manage sialorrhea and thickened saliva,[60] manual and mechanical cough assistance devices,[77] breath stacking,[58] and physiotherapy[78, 79] need to be carefully considered. Common errors that should be avoided include inappropriate use of bronchodilators which results in an increase in anxiety and tachycardia, use of oxygen with or without continuous positive airway pressure (CPAP) and inadequate pressure levels in a bilevel positive airway pressure (BiPAP) ventilator. It addition, it is recommended to seek treatment for bronchial secretions and thick saliva as soon as symptoms occur.[80]

Respiratory, nutritional, and systemic disease conditions tend to overlap and lead to catastrophic results (*e.g.* emergency intubation). In this respect, multidisciplinary ALS clinical programs may help evaluate the patients from all clinical perspectives. This will be of help to choose the best health assistance, offer excellent rehabilitation programs[44, 81] and help solve logistical problems usually occurring at the late stages of the disease.

Whether in ALS exercise is beneficial or harmful is still debated. Case series and case-control studies suggest that intense exercise might be a possible risk factor for ALS.[82-85] Yet other studies failed to confirm these results.[86] Presumably, environmental factors (diet and supplements, pesticides in football fields or brain injuries) may help explain the association between exercise and increased risk for ALS.[83, 87, 88] Strenuous exercise such as cycling or playing basketball does not seem to be a trigger for the disease.[83] Another unsolved clinical question is about the potential therapeutic role of respiratory muscle training in ALS.[46] If on one side physical exercises appear to be safe, clinical evidence on their efficacy is still lacking.[46]

Finally, there is some initial evidence that home-monitoring programs applied to patients under NIPPV or invasive mechanical ventilation are useful not just to achieve a good clinical control, but also to reduce hospital consultations[77, 89-91] and health costs.[46]

Future directions

There is some new evidence that ultrasound examination may be useful to assess patients with ALS. Chest ultrasound are now well known to identify pleural and parenchymal abnormalities in several respiratory diseases,[92-95] and to assess diaphragmatic function.[96-99] The latter is conducted by measuring the diaphragmatic thickness and the respiratory excursions during tidal breathing and at maximal inspiration.[96, 100-102] Recently, diaphragmatic ultrasound has been validated in mechanically ventilated patients.[103] Two recent studies using ultrasound detection of muscle fasciculations documented that this may help improve the diagnostic accuracy of the disease.[104, 105] Other studies conducted in patients with ALS with and without bulbar dysfunction documented that ultrasound can be applied to the diaphragm to assess its function.[98, 106] More studies are however, required to select the parameters that best identify the level of dysfunction according to the severity of the disease.[107]

Conclusions

Progressive respiratory muscle weakness is a clinical hallmark of ALS leading to respiratory failure and death. Its objective assessment is the main part of the comprehensive approach to the

disease and is grounded on the measurement of dyspnea and respiratory muscles strength such as SNIP, MIP and MEP, and its spirometric surrogates such as VC. If the former functional tests are sensitive indicators of the severity of the disease in its early stages, VC finds more practical application late even because of the greater ease of execution. In any case, the ultimate goal of the clinical and functional assessment within a strict follow-up program is to identify the right time for cough assistance and ventilator assistance.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Manuscript accepted: November 15, 2018. - Manuscript received: November 12, 2018.