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*REVIEW*

# Assessment and monitoring of ventilatory function and cough efficacy in patients with amyotrophic lateral sclerosis

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**ABSTRACT:** ***Assessment and monitoring of ventilatory function and cough efficacy in patients with amyotrophic lateral sclerosis. A. Chetta, M. Aiello, P. Tzani, D. Olivieri.***

**Assessing and monitoring respiratory muscle function is crucial in patients with Amyotrophic Lateral Sclerosis, since impaired function can lead to either ventilatory failure or respiratory tract infection. Spirometry, diffusing capacity of the lung, breathing pattern, sleep study, blood gas analysis and respiratory muscle strength tests, as well as cough peak flow and cough expiratory volume measurements can provide relevant information on ventilatory function and cough efficacy. With regard to respiratory muscle strength testing, the rational approach consists in starting with volitional and non-invasive tests and later using invasive and non-volitional tests.**

**This review focuses on both ventilatory and respiratory muscle strength testing, in order to undertake a timely treatment of respiratory failure and/or impaired cough efficacy. So far, the current literature has not highlighted any gold standard which stipulates when to commence ventilation and cough support in patients with Amyotrophic Lateral Sclerosis. A composite set of clinical and functional parameters is required for treatment scheduling to monitor lung involvement and follow-up in these patients.**

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***Keywords: Amyotrophic lateral sclerosis, respiratory muscle tests, cough, ventilatory failure, non-invasive positive pressure ventilation.***

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## Introduction

Respiratory muscle function is crucial to support ventilation and ensure the cough reflex. Impairment of this function can lead to either ventilatory failure and/or respiratory tract infections. In Amyotrophic Lateral Sclerosis (ALS), as well as in neuromuscular diseases in which respiratory muscles are involved, prognosis is strictly related to the involvement of these muscles and to the progressive impairment of pulmonary function [1]. The assessment and monitoring of respiratory muscle function is clinically relevant in patients with ALS. Furthermore, the prompt detection of respiratory muscle dysfunction in ALS patients has relevant therapeutic consequences.

Spirometry, lung volume measurement and diffusing capacity of the lung can provide useful information on respiratory muscle function. However, to specifically study the respiratory muscle strength, volitional or non-volitional tests, which measure respiratory muscle strength as the pressure caused by muscle contraction, should be performed [2] (tab. 1). Furthermore, cough efficacy should be evaluated by expiratory muscle strength tests and expiratory flow and volume measurements during a voluntary cough.

This review specifically addresses the assessment and monitoring of respiratory muscle function in patients suffering from ALS. The role of the different tools to assess and monitor the ventilatory function and cough reflex is reviewed. Moreover, a rational sequence of non invasive and invasive tests for respiratory muscle strength is suggested and, the timing of therapeutic interventions for ventilatory failure and inefficient cough is also considered.

## Spirometry, lung volumes, diffusing capacity of the lung and blood gas analysis

Measurement of vital capacity (VC) may be useful for evaluating respiratory muscle impairment in ALS patients. VC can be reduced due to an impairment in either inspiratory or expiratory muscles. The simplicity of the test represents its biggest advantage, especially when a series of measurements are required over a long period of time. In ALS patients, repeated measurement of VC is a useful method to evaluate the progression of the disease. When respiratory muscle weakness is acute and progressive, the relationship between strength and VC is not linear and great weakening might precede the reduction of VC [3].

Later, further impairment of muscle strength causes important decreases in VC which results in ventilatory failure [4]. In patients with chronic respiratory muscle impairment, changes occur in the

Table 1. - Volitional and non-volitional respiratory muscle strenght tests

| | Volitional | Non volitional |
|---|---|---|
| **Total inspiratory strength tests** | | |
| | Maximal Inspiratory Pressure (*MIP*)<br>Sniff Nasal Pressure (*SNIP*)<br>Sniff Esophageal Pressure (*Sniff Pes*) | |
| **Total expiratory strength tests** | | |
| | Maximal Expiratory Pressure (*MEP*)<br>Whistle Mouth Pressure (*Pmow*)<br>Cough Gastric Pressure (*Cough Pgas*) | Gastric Pressure by Thoracic Inferior Nerve Roots Stimulation (*TwPgas*) |
| **Diaphragm strength tests** | | |
| | Sniff Transdiaphragmatic Pressure (*Sniff Pdi*) | Transdiaphragmatic Pressure by Phrenic Nerve Stimulation (*TwPdi*) |

rigidity of the chest wall and pulmonary compliance and the relationship between respiratory muscle strength and VC becomes more linear [4]. Generally, VC may decrease down to 30% of its predicted value before hypercapnia appears unless there is a further load on the respiratory system [3].

Assessment of VC should be performed in both seated and in supine position [5]. In patients with important weakness of the diaphragm, a significant decrease in this parameter is common in the supine position. In these patients, the weakened diaphragm is sucked into the chest while the anterior abdomen wall moves towards the interior (i.e. paradoxical abdominal movement). These patients have important orthopnaea and decreased VC in the supine position. In case of complete bilateral paralysis of the diaphragm, the VC in upright posture might vary between 30 and 65% of the predicted value and be halved in the horizontal position [5]. Measurement of VC in the supine position might provide important supplemental information on diaphragm function. In ALS patients, it has been proven that this parameter is significantly correlated to transdiaphragm pressure (Pdi) since a VC value in the supine position less than 75% of the predicted value can forecast a Pdi value below 70 $cmH_2O$ with specificity and sensitivity equal to 100% [6].

The major disadvantage of VC, as a measure of respiratory muscle strength, is that it might be modified by other diseases, and if these diseases coexist, it is very difficult to estimate the real contribution of each illness. Moreover, measurement of VC is voluntary and may be difficult to perform under particular circumstances, such as in intensive care units [7].

In addition to VC, other parameters of pulmonary function might indicate respiratory muscle weakness [8]. The ratio of residual volume/total lung capacity (RV/TLC) is often increased [8]. Diffusing lung capacity for CO (DLCO) is generally reduced, but if corrected for alveolar volume, it can be either normal or increased, and considered to be a marker of respiratory muscle weakness in patients with restrictive respiratory defect patterns [9]. Also the shape of the flow-volume curve might be changed in patients with significant respiratory muscle weakness. In these cases, reduction of maximal inspiratory flow might cause a truncated inspiratory curve similar to the one observed in patients with upper airway obstruction [10].

The modifications in blood gas analysis values, which occur in ALS, are not specific to the disease. Patients with respiratory muscle weakness usually present slight to moderate hypoxemia while hypercapnia occurs later. Generally, in neuromuscular diseases, hypercapnia is developed when respiratory muscle strength decreases down to a quarter of its normal value, unless other concomitant diseases exist [11]. Venous serum chloride and bicarbonate measurements can also provide useful information about respiratory status and prognosis in ALS patients [12]. Raised bicarbonate and low chloride were associated with the presence of respiratory symptoms suggesting respiratory muscle weakness [12].

With respect to bulbar involvement, it has been shown that ALS patients with bulbar signs showed lower values of spirometry and higher values of $PaCO_2$, when compared to patients without bulbar signs [13]. A more severe hypoventilation and restrictive ventilatory defect in bulbar ALS patients

are due to the upper airway muscle weakness and aspiration linked to bulbar involvement, leading to a lower compliance of the lung, an increased work of breathing and a respiratory pattern progressively more and more shallow [14].

It should be noted that the bulbar muscle integrity can be estimated in ALS patients, by evaluating the difference between maximum insufflation capacity (MIC) and VC. The MIC is determined by measuring spirometrically the largest volume of air that a patient can hold with closed glottis [15].

To obtain MIC, the patient air-stacks via a mouthpiece consecutively delivered volumes from a volume-cycled ventilator or manual resuscitator [15]. The patient stacks the consecutively volumes with a closed glottis until the lungs are maximally expanded [15]. In non bulbar ALS patients, the VC decreases with time, but the MIC can be preserved or increased before declining [15].

## Breathing pattern and sleep study

In patients with neuromuscular diseases, hypoxemia and hypercapnia might be relevant during sleep, particularly during the rapid eye movement (REM) phase, when the respiratory drive is reduced [16]. So, in case of either suspected or diagnosed muscle weakness, studying the sleep pattern might be important to evaluate respiratory failure at its onset [16]. Evolving hypoventilation during sleep causes bicarbonate retention, loss of sensitivity to $CO_2$ and progressive hypercapnic respiratory failure.

Sleep-disordered breathing is frequently encountered in patients with ALS [16]. Respiratory and upper airway muscle weakness, as well as abnormalities of ventilatory control all occur in ALS patients and serve to enhance the likelihood of sleep-disordered breathing [16]. ALS patients with sleep-disordered breathing complain of restless sleep, nightmares, enuresis and frequent arousals. Other less obvious symptoms of sleep-disordered breathing include poor appetite, morning headache and cognitive and intellectual impairment. The nature of sleep-disordered breathing in ALS patients reflects the distribution of respiratory muscle involvement [17]. When patients have severe diaphragm dysfunction, suppression of intercostals and accessory muscles during REM sleep leads to hypoventilation [17]. If diaphragm strength is preserved, but the upper airway or intercostal muscles are weak, obstructive apneas or hypopneas are more likely to occur [17]. In a large group of ALS patients, Gay *et al.* [1] reported a mean Apnea Hypopnea Index (AHI) of 11.3 events/h, even if the principal cause of nocturnal desaturation was hypoventilation. Other studies confirmed that the commonest form of sleep-disordered breathing in ALS patients was hypoventilation due to diaphragm weakness [18, 19].

Moreover, no significant relations have been reported between bulbar involvement and both the severity of sleep-disordered breathing and the type of sleep-disordered breathing, such as central or obstructive apnea [18, 19, 20].

In the early stage of the disease, overnight oximetry, which can be performed at the patient's home, is useful to exclude oxygen desaturation. In case of nocturnal desaturations, full polysomnography, performed in hospital, can accurately determine their causes. In ALS patients, obstructive events need to be distinguished from hypoventilatory desaturations because they may simply require CPAP therapy to maintain upper airway patency. Mixed obstructive and hypoventilatory states may require inspiratory support with non invasive positive pressure ventilation (NIPPV) combined with a positive end expiratory pressure.

## Maximal mouth pressures

The easiest test available to assess either inspiratory or expiratory muscle weakness is to measure the maximal mouth pressures [2]. To obtain Maximal Expiratory Pressure (MEP), patients perform a maximal static expiratory effort from TLC against a valve [21]. Maximal Inspiratory Pressure (MIP) is measured by performing a maximal static inspiratory effort from RV [21].

There are several available portable devices for measuring mouth pressures, thus, it is possible to measure them even in bedridden patients [2]. Different mouthpieces are used; the circular one, made of rubber, is placed around the mouth and may produce higher MEP and MIP values than the one kept tightly between the teeth, the former is also better tolerated by the patients [22]. Under special circumstances, such as in patients with bulbar weakness, who cannot tighten their lips around the mouthpiece, it may be necessary to use facial masks, which link the patient to either the spirometer or the pressure measuring device [23].

The majority of patients can achieve reliable MEP and MIP measurements, and when high values are found, muscle weakness is excluded [2]. However, it can be difficult for some patients to perform this manoeuver, thus, the range of normal values is quite wide and this reduces the clinical value of MEP and MIP measurements as indicators of respiratory muscle weakness [2]. In general, MEP and MIP values higher than 100 $cmH_2O$ and 80 $cmH_2O$, respectively, exclude a clinically relevant respiratory muscle weakness [24]. On the other hand, it is difficult to establish whether low values are the result of muscle weakness or due to the patient's inability to correctly perform the test.

Acceptable results are very difficult to obtain from patients with severe weakness of either superior limbs or facial muscles. Patients with either normal VC or high values of maximal mouth pressures do not present any problems with respiratory muscle strength.

On the other hand, patients with reduced VC and low MEP and MIP values need further tests to assess respiratory muscle weakness [2].

## Oesophageal and nasal *sniff* pressures

If respiratory muscle weakness is hypothesized after performing pulmonary function tests and

measuring maximal mouth pressures, the next step is to measure oesophageal pressure by means of a balloon catheter. After placing the catheter correctly down the oesophagus, the patient is asked to perform a sharp, maximal and short (less than 0.5 seconds) *sniff* [2]. Generally, the *sniff* manoeuver is easily performed and the patients manage to repeat the test without tiring, so that the test results are reproducible. *Sniff* Pes reflects inspiratory muscle strength better than MIP [25]. Furthermore, a significant number of patients considered to have respiratory muscle weakness because of low MIP values, end up having normal *sniff* Pes values. A *sniff* Pes value greater than 80 $cmH_2O$ in men and 70 $cmH_2O$ in women excludes significant inspiratory muscle weakness [26].

The negative pressure produced during the *sniff* Pes manoeuver reflects the strong contraction of inspiratory muscles and the high flow resistance in the nose. If mouth, nasopharyngeal and oesophageal pressures are measured at the same time during a *sniff* manoeuver, their values will be quite similar [27]. When pressure is measured by means of a catheter placed in a nostril using a plug which adheres to the nasal mucosa, the *sniff* value is similar to the one measured in the esophagus [28]. Thus, *sniff* nasal pressure (SNIP) is a non-invasive test which provides useful information, like *sniff* Pes.

SNIP measurement is important for assessing patients, even if it may be less reliable in those with concomitant chronic obstructive pulmonary disease (COPD) because of an incomplete transmission of pleural cavity negative pressure to the nose during the sharp *sniff* manoeuver. Normal reference values for SNIP have been reported [29]. SNIP values greater than 60 $cmH_2O$ usually exclude inspiratory muscle weakness [26]. It has been recently demonstrated that in ALS patients, a SNIP value less than 40 $cmH_2O$ was significantly related with nocturnal hypoxemia and survival [30]. During the process of diagnosing respiratory muscle weakness, it is rational to perform a SNIP manoeuver and proceed to *sniff* Pes measurement only if the SNIP value is low.

## *Sniff* transdiaphragmatic pressure

When inspiratory muscle weakness is proven by a low *sniff* Pes value, further testing by measuring the transdiaphragmatic pressure (Pdi) may better assess the diaphragm function [2]. This test requires two balloon catheters - one is placed in the oesophagus and the other in the stomach. Pdi is obtained by subtraction of Pes from gastric pressure (Pgas). In the past, diaphragm strength was assessed by measuring Pdi during maximal static efforts. However, the values ranged widely in normal subjects. Hence, the Pdi results obtained by a *sniff* manoeuver are considered to be more reliable [31] and *sniff* Pdi is also highly reproducible.

Thus, *sniff* Pdi is an excellent test for assessing diaphragm weakness and to follow its progress. The accurate measurement of diaphragm strength by means of *sniff* Pdi has confirmed that orthopnaea, paradoxical abdominal movement and a significant decrease of VC in the supine position occur when transdiaphragmatic strength decreases down to 30% of its normal value [32]. A *sniff* Pdi value >70 $cmH_2O$ in females and >100 $cmH_2O$ in males excludes a significant respiratory muscle weakness [26]. *Sniff* Pdi as well as *sniff* Pes measurements are probably the most accurate tests of respiratory muscle weakness that predict ventilatory failure in non-bulbar ALS patients [33]. A disadvantage of this test is that it is invasive and it depends on the patient's cooperation.

## Cough gastric pressure, whistle mouth pressure and cough peak flow and volume

As with MIP, some patients find the MEP test an unnatural and difficultly performed manoeuver [2]. Consequently, the range of normal MEP values is wide. A high MEP value reliably excludes expiratory muscle weakness while a low value can be difficult to interpret. Therefore, in the case of a low MEP value, further techniques are required to exclude expiratory muscle weakness and an ineffective cough.

Patients consider maximal voluntary cough, as well as *sniff*, a natural manoeuver, which can be performed repeatedly without tiring. In many patients, the information obtained by *cough* Pgas is as useful as that obtained by MEP [34]. However, a big number of patients have low MEP values and normal *cough* Pgas values [34], thus, if low MEP values are found, it is proper to perform *cough* Pgas measurements in order to exclude or confirm expiratory muscle weakness. *Cough* Pgas is measured using a balloon catheter passed per nasally, with the tip of the balloon placed in the stomach that is approximately at 70 cm from the nostril. The test consists in performing maximal cough until no further increase of *cough* Pgas is observed. On the whole, *cough* Pgas is considered to be an excellent test for assessing expiratory muscle strength and, despite its recent introduction to the field of tests to evaluate respiratory muscles, it might be clinically relevant [34]. In normal subjects, *cough* Pgas values are, on average, higher than 97 $cmH_2O$ in females and 132 $cmH_2O$ in males [34]. A disadvantage of this test consists in its invasiveness since a balloon catheter is placed in the stomach.

Recently, in ALS patients another non-invasive test has been introduced which may provide a measure of expiratory muscle strength comparable to that of *cough* Pgas. This test, called whistle mouth pressure (PmoW), consists of recording mouth pressure while patients perform a short, sharp blow, as hard as possible, through a device which offers resistance and produces a whistle [35]. The use of PmoW requires further evaluation, but it is likely to be a useful additional test.

Cough efficacy can be assessed by means of cough peak flow (CPF) (L/min) and cough expiratory volume (CEV) (L). During this test, the subjects perform voluntary maximal cough into a tightly fitting face mask connected to a spirometer in order to obtain CPF and CEV measurements

[36]. CPF evaluation is clinically relevant and it can be considered to be an overall parameter of cough efficacy. Normal cough is a sequence of three steps [37]. The first step consists in the complete abduction of the arytenoid cartilages and the vocal cords and the contraction of the inspiratory muscles and diaphragm, so as to inspire at 85-90% of TLC. The second step consists in the closure of the glottis, which is complete and rapid (0.2 seconds approximately). The opening and closure of the glottis presuppose very well functioning larynx muscles. Finally, the third step is characterised by the contraction of the intercostal and abdominal muscles, which causes high intrapleural pressure values, up to 140 mmHg, when the glottis is closed. This step ends with the glottis opening, which causes chest decompression and produces CPF values of 360-1200 L/min and CEV values usually greater than 1.5 L.

When the CPF value is <270 L/min, the removal of respiratory tract secretions is not efficient and the patients are at risk for respiratory failure [38]. This value is considered to be a threshold value under which cough is considered to be ineffective. Up to now, no data has been published on the clinical relevance of the CEV measurement.

## Transdiaphragmatic and gastric pressure measurements by magnetic stimulation

All the tests described so far are useful to assess respiratory muscle strength, however, to ensure its performance, the patient's cooperation is needed. Unfortunately, it is difficult for some patients to achieve maximal voluntary efforts and it is not always possible to obtain good cooperation, such as in patients with severe disease or with bulbar involvement, confused or in the intensive care unit. Under those circumstances, it is necessary to perform non-volitional tests to evaluate respiratory muscle strength. The most important available test consists in measuring Pdi after stimulation of the phrenic nerves (TwPdi). This technique consists in positioning a balloon catheter in the oesophagus and another one in the stomach, as for the *sniff* Pdi manoeuver.

The phrenic nerves can be stimulated by superficial electrodes placed on the neck. Then it is possible to record diaphragm electromyography and Pdi simultaneously [39]. Electrical bilateral supramaximal stimulation can be achieved in normal subjects but it is more difficult to use this technique in patients. In practice, it is often difficult to locate the phrenic nerves, reach the maximal stimulation and obtain reproducible results [2]. So, the electric stimulation of the phrenic nerves has been a useful but imperfect tool over the years. Availability of magnetic stimulators has improved our capability to obtain acceptable phrenic nerve stimulation. Both phrenic nerves can be stimulated by a large, circular, magnetic coil placed on the back of the neck at the medial line over C7 [40]. Alternatively, each phrenic nerve can be stimulated individually by smaller eight shaped coils placed over the phrenic nerves in the anterolateral region of the neck [41, 42]. The normal TwPdi at FRC is approximately 10 $cmH_2O$ with unilateral anterior magnetic stimulation, while with bilateral stimulation it is 25 $cmH_2O$ [26].

Although it is possible to electrically stimulate the abdominal muscles, it is easier to use magnetic stimulators. Magnetic stimulation, by means of a large circular coil placed on the back, over the spine at the level of T10, can activate the abdominal muscles and their strength can be measured as a pressure developed in the stomach (TwPgas) [43].

TwPgas is reproducible and can be used to assess abdominal muscle fatigue in case of exaggerated load [43]. However, TwPgas assessed by magnetic stimulation, using the technique currently available, is not supramaximal, thus it cannot provide an accurate evaluation of abdominal muscle strength. Moreover, this technique is invasive and requires a balloon catheter in the stomach.

## Timing for ventilatory support and secretion removal

To evaluate respiratory muscle strength it is proper to start by performing simple, non invasive tests and then proceed with invasive tests if necessary. Therefore, if vital capacity is normal in the supine position, a relevant respiratory muscle weakness is unlikely [12]. However, if vital capacity is low, it is reasonable to measure both maximal inspiratory and expiratory pressure. If mouth pressures are normal, respiratory muscle weakness is excluded, but if their values are low, it is advisable to investigate further, as reported in figure 1.

Testing ventilatory function as well as respiratory muscle strength can provide useful information on the management of patients affected by ALS. In particular, it allows clinicians to promptly treat respiratory failure and impaired cough efficacy in these patients. NIPPV has been shown to relieve symptoms of alveolar hypoventilation and improve quality of life for ALS patients [44].

The current guidelines of the American Academy of Neurology recommend using NIPPV in patients with ALS as soon as the first respiratory symptoms occur or if VC reduction is at least 50% of predicted [45]. However, a poor correlation between VC and symptoms, respiratory muscle strength and the duration of night oxygen desaturation less than 90%, has been described [46]. Many patients can be symptomatic at near normal VC and manifest evidence of nocturnal hypoxemia [47]. Moreover, in ALS patients, it is has been proven that VC values can vary between 16 and 70% of those predicted at the time when hypercapnia ($PaCO_2 \geq 45$ mmHg) or orthopnaea occur [48].

A European consensus document recommends NIPPV in patients with neuromuscular disorders and a daytime $PaCO_2 \geq 45$ mmHg [49]. However, daytime blood gas changes can occur later than ventilatory defects, especially in the case of a

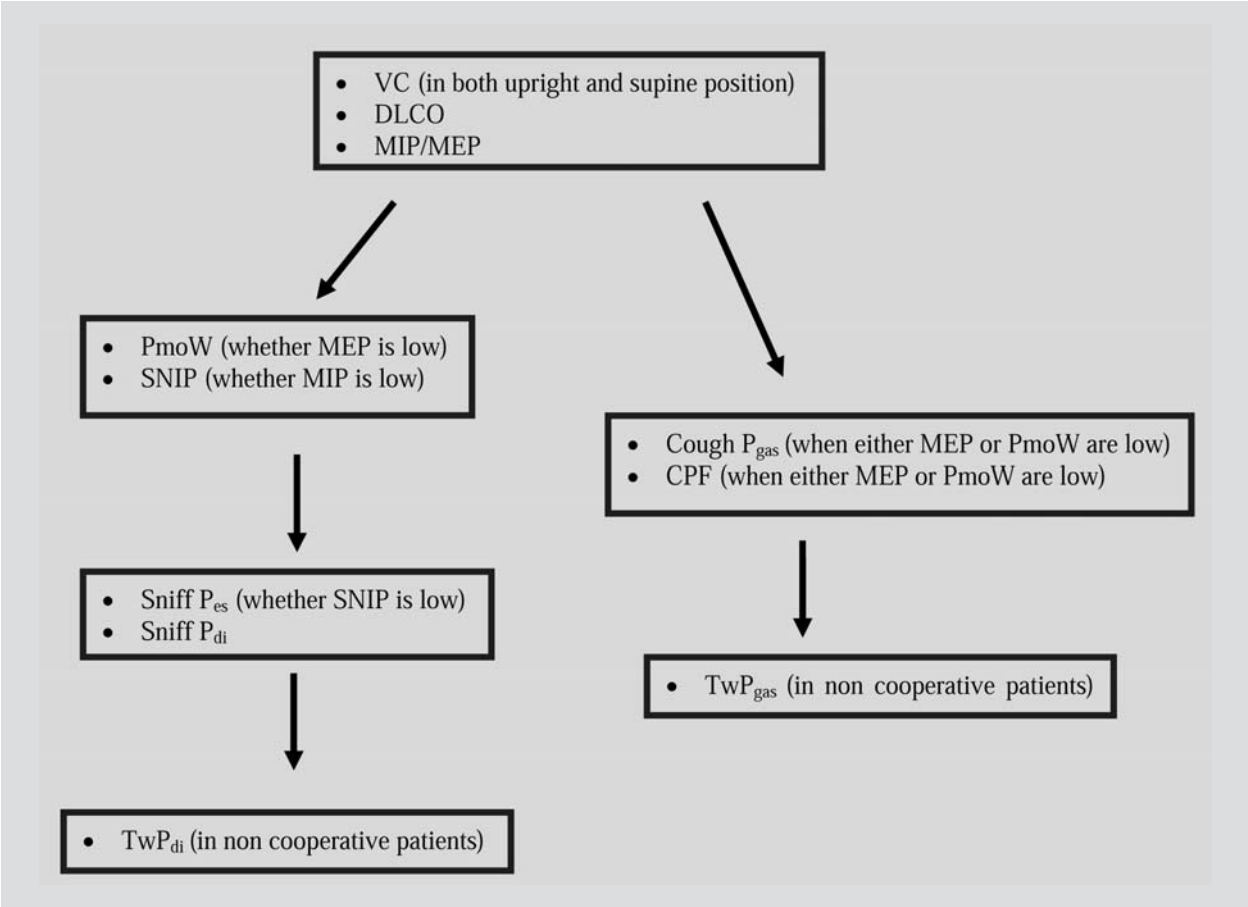


Fig. 1. Sequence of tests to assess respiratory muscle strength.
VC = Vital Capacity, MIP = Maximal inspiratory pressure, MEP = Maximal expiratory pressure, PmoW =Maximal whistle mouth pressure, SNIP = Sniff nasal pressure, Pes = Oesophageal pressure, Pdi = Transdiaphragmatic pressure, TwPdi = Magnetic stimulation transdiaphragmatic pressure, Cough Pgas= Cough gastric pressure, CPF = Cough peak flow, TwPgas = gastric pressure by magnetic stimulation.

rapidly progressive neurological disease, such as ALS [50]. Hence, sleep study allows early detection of respiratory muscle impairment in patients affected by ALS. A nocturnal oxygen desaturation of less than 88%, which lasts ≥5 consecutive minutes, is considered to be early proof of diaphragm impairment (51). Furthermore, a nocturnal oxygen saturation ≤80% is predicted by a MIP decrease ≤ 60 $cmH_2O$ with sensitivity equal to 86%. Hence, MIP can be considered as a marker of nocturnal desaturation [1].

Unfortunately, there is no gold standard which stipulates when to commence NIPPV in patients with ALS. However, it has been demonstrated that patients affected by ALS who made early use of NIPPV, that is with nocturnal desaturation <90% for a minute, had a better quality of life than patients who used NIPPV in the standard way, that is with VC<50% of predicted [46]. Furthermore, both improved quality of life and life expectancy have been observed in patients with ALS who start NIPPV treatment when at least one of the following criteria appears: orthopnaea, daytime sleepiness with Epworth Sleepiness Scale (ESS) >10, Apnoea-Hypopnoea Index (AHI) >10/hour of sleep, respiratory muscle weakness defined as MIP and SNIP<80% of predicted, daytime $PaCO_2$>45 mmHg in spontaneous ventilation, and nocturnal oxygen desaturation (defined as a $SpO_2$ value ≤90% for ≥5% of the total time) [52]. In this study, predicted MIP and SNIP values were obtained according to Wilson *et al*. (53) and Uldry and Fitting [29] reference equations, respectively. Finally, in a large group of ALS patients, it has been recently confirmed that an early systematic respiratory evaluation improves the indication of NIPPV treatment with benefits not only in terms of survival time, especially in patients without bulbar involvement, but also with respect to decision making [54]. Up to now, no data has been published on the usefulness of both volitional and non-volitional Pdi measurements with respect to the timing of NIPPV treatment.

In patients affected by ALS, respiratory muscle weakness is associated with the patients' inability to produce supramaximal flows during cough, so dynamic compression of the airway is impaired and cough efficacy is reduced [55]. Experts in this field recommend the use of expiratory aids in addition to ventilatory support to remove secretions [56]. Furthermore, in some ALS patients, expiratory muscle weakness may occur before inspiratory weakness, and supportive secretion removal precedes NIPPV. Particular attention should be paid to patients with bulbar impairment, since it can result in aspiration that overwhelms a poor cough effort. In retrospective studies it has been shown that the use of inspiratory and expiratory support in patients with neuromuscular dis-

eases reduces the rate of hospital admissions for respiratory problems [57] and improves life expectancy [58].

Expiratory aids consist of training to improve MIC by air stacking [59] and/or assisted cough, either manually or through a mechanical insufflation-exsufflation (MI-E) device [36, 60]. The inclusion criterion for air stacking training includes a fairly preserved bulbar function so that glottic closure can allow the MIC to exceed the VC. In clinical and rehabilitation settings, MI-E devices are used applying pressures from 40 to -40 $cmH_2O$, by customizing them to each patient [58, 59, 61]. MI-E devices effectively clear secretions in ALS patients [45] and their clinical value can be explained by the fact that they can generate expiratory flows >160 L/min [62]. Recently, it has been also demonstrated that MI-E via a tracheostomy tube is more effective in clearing airway secretions than conventional suctioning in ventilator-dependent ALS patients [63].

In patients with ALS, it has been shown that ventilatory support added to cough support, when CPF is less than 270 L/min, can prolong survival and postpone tracheotomy (58). However, when CPF values are <160 L/min, bulbar dysfunction is particularly severe and patients are not able to remove respiratory tract secretions [64], so intubation may be required. Accordingly, in ALS patients CPF should be checked regularly for early identification of ineffective cough, and later to assess the effectiveness of breath stacking and manually or mechanically assisted cough.

Based on the current literature, an algorithmic approach to both assessment and monitoring of ALS patients and timing of therapeutic interventions before ventilatory failure and inefficient cough is shown in figure 2. At the time of the diagnosis, a patient with ALS should perform a systematic respiratory evaluation consisting in spirometry, respiratory muscles testing, cough efficacy test, blood gas analysis and nocturnal oximetry. In pres-

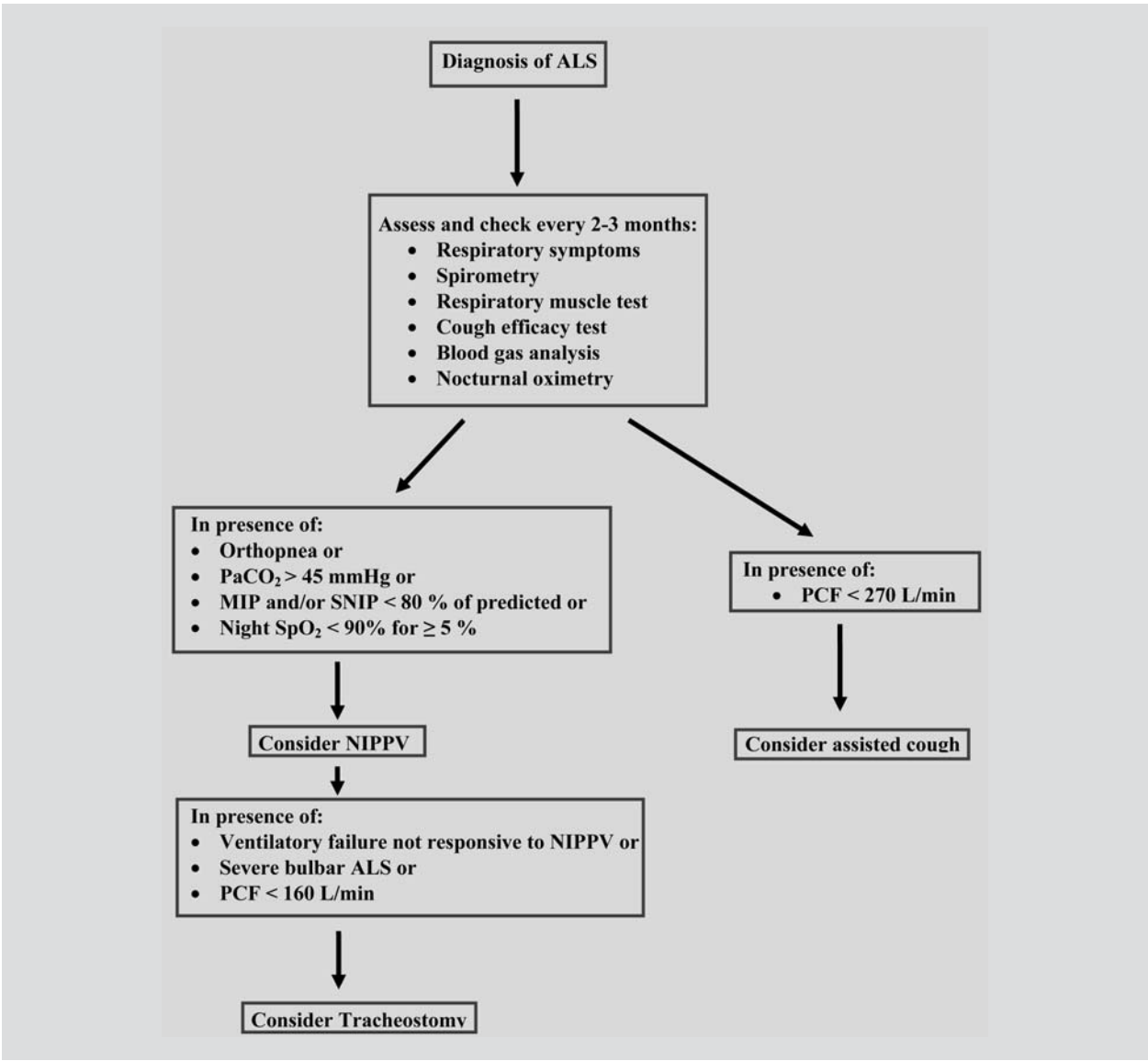


Fig. 2. Algorithmic approach to assessment and monitoring of ALS patients and timing of therapeutic interventions before ventilatory failure and inefficient cough in patients affected by ALS.
VC = Vital Capacity, MIP = Maximal inspiratory pressure, MEP = Maximal expiratory pressure, PmoW = Maximal whistle mouth pressure, SNIP = Sniff nasal pressure, Cough Pgas = Cough gastric pressure, CPF = Cough peak flow, NIPPV = Non invasive positive pressure ventilation.

ence of either orthopnea or $PaCO_2$ greater than 45 mmHg or MIP and/or SNIP less than 80% of predicted value or nocturnal oxygen saturation less than 90% for ≥5% of the total time, a NIPPV should be considered for the patient. In addition, if the PCF value is less than 270 L/min an assisted cough should be considered. Lastly, in presence of either ventilatory failure not responsive to NIPPV or severe bulbar involvement or PCF less than 160 L/min a tracheostomy ventilation should be also considered. Clinical and ethical problems due to particular procedures, such as NIPPV or tracheostomy, can be solved by a multiprofessional approach involving a multidisciplinary team.

## Conclusions

In patients with ALS, pulmonary complications are the main cause of death [65], therefore an accurate assessment of the lung function should be performed in these patients. Spirometry, diffusing capacity of the lung, blood gas analysis, respiratory muscle strength tests, as well as cough peak flow and cough expiratory volume measurements can provide relevant information on ventilatory function and cough efficacy. Regarding respiratory muscle strength testing, the rational approach consists in starting with volitional and non-invasive tests and later using invasive and non-volitional tests, which should be considered in selected patients.

Afterwards, a close clinical surveillance of respiratory problems, such as recurring acute bronchitis, drowsiness or orthopnea is essential to evaluate the progressive lung involvement in ALS patients [66]. However, timely treatment of pulmonary involvement requires more than the initial clinical evaluation. The functional follow-up should include regular monitoring with simple tests, such as upright and supine VC, maximal inspiratory and expiratory pressures, CPF, diurnal and nocturnal oximetry.

These can be checked at bedside as well as in an outpatient clinic setting. The regular assessment and monitoring of respiratory muscle function and cough efforts are crucial in patients with ALS, in order to successfully manage either ventilatory failure, secretion clearance or respiratory tract infection [67].

Up until now, there has been no gold standard which stipulates when to commence ventilation support in patients with ALS. On the other hand, a composite and wide set of clinical and functional parameters is necessary for a successful approach to the timing of the respiratory failure and/or ineffective cough treatments and their follow-up. Moreover, there is evidence that early assisted ventilation treatment leads to better quality of life and life expectancy, and experts also recommend the use of expiratory aids in addition to ventilatory support to remove airway secretions. However, better designed, randomized and controlled studies are needed to determine the optimal time to start these treatments.

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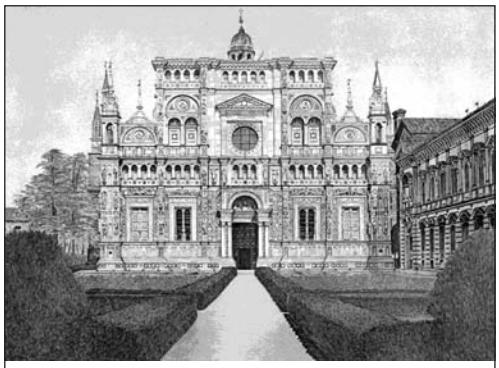

*Pavia - La Certosa*