UNIVERSITÀ DEGLI STUDI DI MILANO

Facoltà di Medicina e Chirurgia

Dipartimento di Scienze della Salute

Corso di Dottorato in Medicina Clinica e Sperimentale

LUNG FUNCTION AND DYSPNEA IN NEUROMUSCULAR DISEASES

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) and similar neurodegenerative disorders are characterized by progressive respiratory decline inevitably leading to respiratory failure. Accurate respiratory function testing, along with dyspnea assessment, are not always easily achievable, but represent key elements for major clinical decision-making.

Dr. Giulia Pellegrino's PhD program was centered on the pathophysiological and diagnostic features of dyspnea and respiratory failure. In the course of her doctorate she produced:

1. a review paper regarding ALS clinical management, that outlined the design of a prospective database that Dr. Pellegrino created for the collection of functional respiratory data in patients affected by ALS followed at Casa di Cura del Policlinico in Milan. **Minerva Med. 2018 Dec;109(6 Suppl 1):11-19. doi: 10.23736/S0026-4806.18.05920-7.**

2. An original research designed to identify the best interfaces to perform the vital capacity measure in patients with and without bulbar impairment, in order to draw clinical indications on how to best perform the maneuver according to the phenotypical presentation. **Respir Med. 2021 Jan;176:106277. doi: 10.1016/j.rmed.2020.106277.**

3. The Italian translation and validation of the Multidimensional Dyspnea Profile (MDP), aimed to provide an important clinical and research tool, to be utilized in future Italian studies on the topic. **Questionnaire available upon request at Mapi Research Trust (mapi-trust.org), accepted on Jan. 14, 2019.**

4. An original research aimed to identify the main causes underlying dyspnea in neuromuscular diseases, by elucidation of the physiological effects of air-stacking through the forced oscillation technique (FOT). **Archives of Physical Therapy and Rehabilitation, accepted for publication on Jan. 19, 2021.**

RIASSUNTO

La sclerosi laterale amiotrofica (SLA) e altri disordini neurodegenerativi con simili tratti clinici sono caratterizzati dal progressivo declino della funzione ventilatoria, che conduce inevitabilmente a insufficienza respiratoria. L'accurata misurazione della funzionalità respiratoria, unitamente alla valutazione della dispnea, sono spesso difficili da ottenere, ma rappresentano elementi chiave per decisioni cliniche maggiori.

Il programma di dottorato della Dr.ssa Giulia Pellegrino è stato incentrato sull'approfondimento delle caratteristiche fisiopatologiche e diagnostiche della dispnea e dell'insufficienza respiratoria. Nel corso del dottorato sono stati prodotti:

1. un *review paper* riguardante la gestione clinica della SLA, che ha delineato il disegno di una banca dati prospettica che la Dr.ssa Pellegrino ha successivamente creato per la raccolta dei dati di funzionalità respiratoria nei pazienti affetti da SLA seguiti alla Casa di Cura del Policlinico, a Milano. **Minerva Med. 2018 Dec;109(6 Suppl 1):11-19. doi: 10.23736/S0026-4806.18.05920-7.**

2. Uno studio originale teso a individuare le migliori interfacce per la misurazione della capacità vitale in paziente con e senza insufficienza dei muscoli bulbari, allo scopo di trarre indicazioni cliniche su come meglio effettuare la manovra a seconda della presentazione fenotipica. **Respir Med. 2021 Jan;176:106277. doi: 10.1016/j.rmed.2020.106277.**

3. La traduzione e validazione in italiano del *Multidimensional Dyspnea Profile* (MDP), uno strumento importante dal punto di vista clinico e di ricerca, che possa essere utilizzato in futuri studi italiani sull'argomento. **Questionario disponibile su richiesta presso Mapi Research Trust (mapi-trust.org), data di accettazione Gennaio 14, 2019.**

4. Uno studio originale mirato a identificare i principali determinant della dispnea nelle malattie neuromuscolari, tramite l'elucidazione degli effetti fisiologici dell'*air stacking* misurati con la tecnica delle oscillazioni forzate (FOT). **Archives of Physical Therapy and Rehabilitation, data di accettazione per la pubblicazione Gennaio 19, 2021.**

CHAPTER I

RESPIRATORY MUSCLE TESTING IN AMYOTROPHIC LATERAL SCLEROSIS: A PRACTICAL APPROACH

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.

INTRODUCTION

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 and other treatments are urgently required. (4) Respiratory symptoms occur late in respiratory involvement and portends decreased survival. (5) In contrast, early assessment of respiratory muscle function may permit a timely recognition of respiratory muscle weakness (see figure 1) and assist in the decision to start non-invasive positive pressure ventilation (NIPPV). Of clinical relevance, survival in patients under NIPPV proved to be significantly higher if NIPPV was initiated early. (6) In addition, respiratory muscle tests provide prognostic information and allow for risk-stratification prior to percutaneous endoscopic gastrostomy (PEG) tube placement. (7) Societal recommendations suggest measurements of vital capacity (VC) over time to quantify respiratory muscle weakness in patients with ALS. (7,8) However, VC has physiological limitations in assessing muscle strength (9) and it is technically challenging in about 20% of patients, mainly for bulbar dysfunction. (10)

Through insights from the landmark study of Polkey et al., (4) we resume key features of respiratory muscle testing and propose a non-invasive approach to help in deciding whether to start NIPPV and other supportive treatments for ALS. Finally, we underline unanswered clinical questions concerning the respiratory management of ALS.

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

The gold standard for the assessment of the respiratory muscle strength is the measurement of the force exerted against an occluded valve. (11) In 1969 Black and Hyatt pioneered the non-invasive assessment of the maximal static inspiratory (MIP) and expiratory pressure (MEP). (12,13) Nowadays, MIP and MEP are non-invasive, readily available, standardized, and economic tests to assess muscle strength. (14) Given the force-length relationship of the lungs, MIP values decreases earlier than lung volumes (27) and it is considered more sensitive than VC in detecting inspiratory muscle weakness (see figure 1). (15) A MIP value more negative than -70 cmH20 for women and -80 cmH20 for men practically excludes clinically relevant inspiratory muscle weakness, while a MEP value below 40 cmH20 is likely to be associated with ineffective cough. (14,16) However, caution should be used in interpreting MIP and < data, as low values may results from a lack of motivation and poor efforts. (17) Measurement of the transdiaphragmatic pressure (Pdi) (18,19) is the test necessary to evaluate 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. (14,18) Due to its invasive nature and the technical challenges involved in collecting and interpreting results, (20) this technique is generally limited to reference centers or physiological research. (4)

In daily practice, clinical assessment and lung volumes measurement may raise the suspicion of respiratory muscle weakness, being a reduction in vital capacity (VC) the most frequent abnormality in muscle weakness. (14,21) VC may be limited by weak inspiratory muscles preventing full inflation and/or weakness of the expiratory muscles impairing expiration (see figure 2). (14) Moreover, a reduction in compliance of the lung and the chest wall have been reported in neuromuscular patients. (8,22) A physiological limitation of spirometry is that a decrease in lung volumes is a relatively late finding when compared to the progression of muscle dysfunction. (9) This is because of the non-linear relationship between volume and pressure. (23) In mild to moderate weakness, VC is in general less sensitive than maximum

respiratory pressures (23) (see figure 1). Moreover, a decrease of VC is non-specific being caused by other restrictive lung diseases. Finally, a practical limitation of spirometry in patients with bulbar impairment is due to mouth leaks and lack of coordinated muscle activity to perform the test. (24)

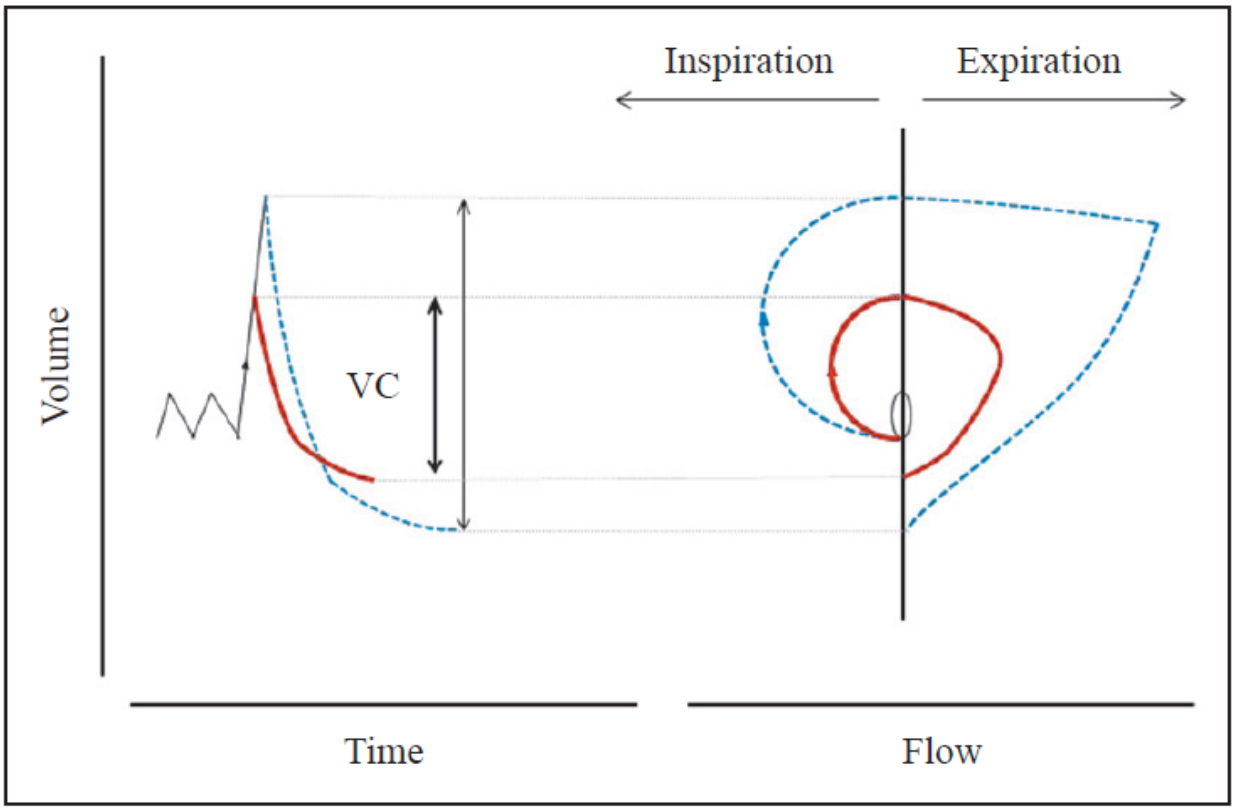

Figure 2. Schematic representation of lung volume in amyotrophic lateral sclerosis plotted against time (left panel) and flow (right panel) during tidal breathing and forced inspiratory and expiratory manoeuvres. Blue and red lines (in the online version) are predicted and observed tracings, respectively. 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 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.11 The sniff nasal inspiratory pressure (SNIP) is measured through a pressure transducer placed in a nostril with the other left unoccluded. (25) SNIP obviates the need of mouth seal, linearly declines with progression of the disease, (26) and has a high predictive power to predict survival. (4) In general, a SNIP <-50 cmH20 for women and <-60 cmH20 for men exclude relevant respiratory muscle weakness. (27) However, SNIP test requires training, (28) and it may have some limitations in patients with bulbar impairment, anatomical abnormalities and nasal congestion. (29)

Cough is a vital reflex that requires the integrity of bulbar, inspiratory and expiratory muscles, (30) 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. In clinical practice, a PCF >160 L/min is sufficient to remove secretions, though values >270 L/min (31-32) may be necessary to clear secretions especially during chest infections. (33)

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.

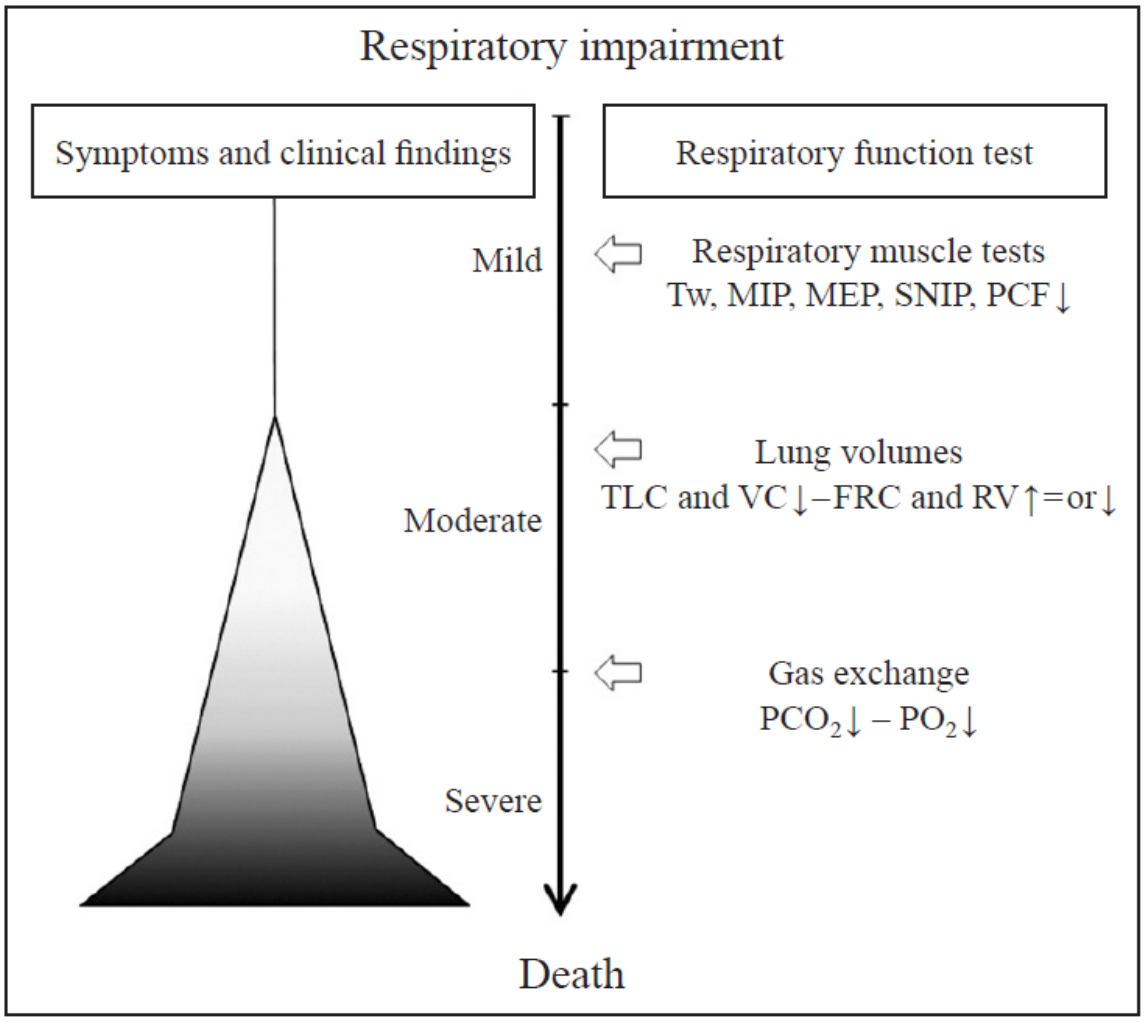

Figure 1. Respiratory tests sensitivity according to amyotrophic lateral sclerosis disease progression.

INDICATIONS FOR NIPPV

The decision to start NIPPV in ALS should include a full evaluation of symptoms with special attention to dyspnea and objective test of respiratory failure. Spirometry is necessary to measure VC and to detect coexisting abnormalities. Diffusing capacity of the lung for carbon monoxide (DLCO) (34) is helpful to rule out unexpected conditions. VC values below 50% of

predicted is considered a threshold to start NIPPV. Yet in two studies NIPPV was initiated when VC was less than 75% or 65% of predicted with significant higher survival. (35)

MIP and SNIP are markers of inspiratory muscles performance. In a recent study, SNIP has been showed to be easier to perform and more feasible than MIP in advanced diseases. (4) MIP values < 60 cmH20 and/or SNIP < 40 cmH20 indicate to initiate 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-off to provide cough assistance. (36) Cough aids may be provided either manually or mechanically according to patient preferences and availability. Decrement below 89% for more than 5 consecutive minutes is a criterion to start NIPPV (37) and predict survival in ALS. (38) In selected cases a full polysomnography may be required. Given that impaired ventilation may worsen during sleep, transcutaneous carbon dioxide and capnography as been used to early detect nocturnal hypoventilation. (39) 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 (see table). (40) ALS presentation with overt respiratory impairment occurs in about 3% of patients and portends reduced survival. (41) Usually, respiratory impairment follows limb or bulbar onset with an asymptomatic involvement of unknown duration (see figure 1). Dyspnea seems to mirror inspiratory muscle weakness and is amid criteria to start NIPPV. (42) Yet, dyspnea at rest is a late finding, as it is the culprit of a relentless progression towards respiratory failure. (40) Given the contribution of the cortical areas in elaborating its perception43, assessing dyspnea is not easy. (44,45) Some patients tend to underestimate dyspnea, partly for reduction in daily activities or fear, despite marked impairment of spirometry (e.g. FVC 38%). (46) Different scores have been proposed to best estimate the symptom. (47) Notably, when performed in the supine position, the BORG score nicely correlate with inspiratory muscle weakness. (47) 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 vital capacity remain 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. (4)

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.

Table I. Advances and unanswered clinical questions in the respiratory management of amyotrophic lateral sclerosis.

In bulbar impairment both the assessment (e.g. VC) and supportive treatment (e.g. NIPPV) are challenging as frequently biased by leaks resulting from a lack of mouth seal. (48) Specific studies are required, starting from shedding light on methods to evaluate the patients with bulbar impairment.

Several supportive therapies are available for patients with ALS. These include symptomatic drugs and specific treatments to manage sialorrhoea and thickened saliva, (49) NIPPV, (50) manual and mechanical cough assistance devices, (51) breath stacking, (52) and physiotherapy. (53)

In evaluation patients with rare diseases, one should avoid the fixation error occurring when one concentrates solely on one aspect of a clinical case. (54) Common errors to be avoided

include: inappropriate use of bronchodilators which results in an increase in anxiety and tachycardia; use of oxygen alone and/or continuous positive airway pressure (CPAP) without inspiratory support; inadequate pressure levels in a bilevel positive airway pressure (BiPAP) ventilator; neglect to perform specific muscle test in addition to spirometry; and, delays in the use of specific treatment, such as respiratory muscle aids, suctioning and other strategies to manage secretion and thick saliva. (55)

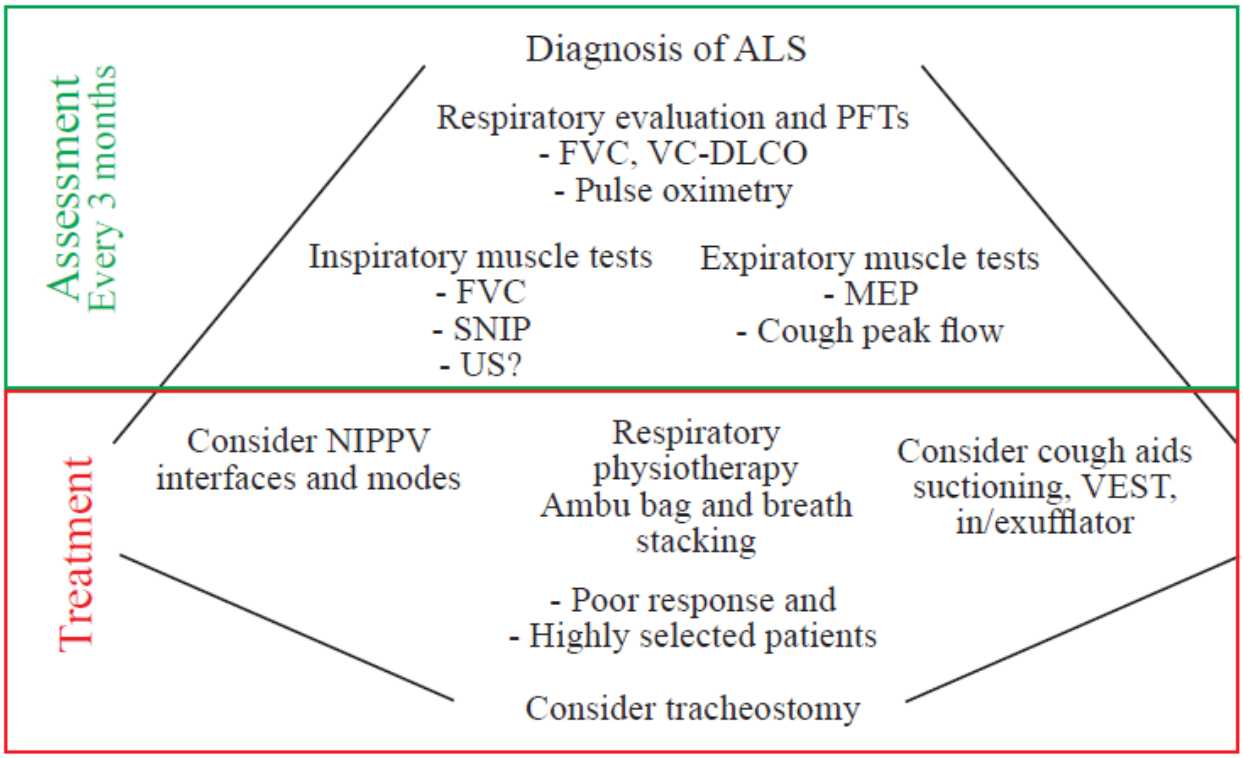

Figure 3. A non-invasive approach to respiratory muscle testing in amyotrophic lateral sclerosis.

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, 56) 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. (57) Yet other studies failed to confirm these results. (42) 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. (42) Strenuous exercise such as cycling or playing basketball does not seem to be a trigger for the disease. (57) Another unsolved clinical question is about the potential therapeutic role of respiratory muscle training in ALS. (42) If on one side physical exercises appear to be safe, clinical evidence on their efficacy is still lacking. (42)

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 (58) and health costs. (42)

FUTURE DIRECTIONS

There is some new evidence that ultrasound examination may be useful to assess patients with ALS. (59) Chest ultrasound are now well known to identify pleural and parenchymal abnormalities in several respiratory diseases, (60) and to assess diaphragmatic function. (61) The latter is conducted by measuring the diaphragmatic thickness and the respiratory excursions during tidal breathing and at maximal inspiration. (62,63) Recently, diaphragmatic ultrasound has been validated in mechanically ventilated patients. (64) Two recent studies using ultrasound detection of muscle fasciculations documented that this may help improve the diagnostic accuracy of the disease. (65) 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. (66) More studies are however, required to select the parameters that best identify the level of dysfunction according to the severity of the disease.

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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CHAPTER II

ITALIAN TRANSLATION AND LINGUISTIC VALIDATION OF THE MULTIDIMENSIONAL DYSPNEA PROFILE

ABSTRACT

Dyspnea is a common source of suffering for patients affected by cardiorespiratory or neuromuscular diseases. The symptom is complex and encompasses different sensory qualities with distinct intensities. The Multidimensional Dyspnea Profile (MDP) is an instrument specifically developed to assess the multidimensional dimensions of the symptom, and it is applicable in both the research and clinical setting. In order to allow its use for Italian speaking populations, we aimed to provide a linguistically validated, Italian translation of the MDP.

We conducted a structured translation and linguistic validation of the MDP questionnaire in accordance to the international guidelines and in cooperation with a specialized company (MAPI SAS, Language Services Unit, Lyon, France). Cognitive interviews on 8 patients were conducted in order to test clarity and understandability of the questionnaire. The multistep process was enriched by several quality checks which led to a translation conceptually equivalent to the original version (American English).

A final certified copy linguistically validated Italian translation of the MDP is now available. It measures the intensity of the breathing discomforts in five sensory qualities and assess its intensity and potential reactions.

W e here provide an Italian translation and linguistic validation of the MDP. This instrument, allows the assessment of dyspnea in both its sensory and emotional aspects, therefore representing a valuable method for research and therapy purposes.

INTRODUCTION

Dyspnea is the subjective feeling of breathing discomfort, a common symptom of cardiorespiratory and neuromuscular diseases (1, 2). Dyspnea is a source of suffering for patients and caregivers, and a strong predictor of disease severity and mortality (2-4). As with pain, dyspnea has been shown to be the result of different afferent mechanisms, and likely, a more sophisticated approach to the symptom would warrant better treatment options. However, the classical methods employed to measure it (such as the Visual Analog Scale (VAS) (5), the Borg scale (6), or the Medical Research Council (MRC) scale (7) are not designed to assess the diverse dimensions of dyspnea. In fact, unidimensional scales can establish the intensity of the symptom, but not the affective dimension, which plays a fundamental role in the overall impact on the patient's life (2).

The Multidimensional Dyspnea Profile (MDP) is an instrument which assesses dyspnea in both its sensory and affective dimensions, thus providing in-depth information regarding the quality and the overall physical and emotional burden affecting the patient (8). It is not disease-specific, and it has been recently validated in different cardiorespiratory diseases (9) and in chronic obstructive pulmonary disease (COPD) (10). Another interesting feature of the questionnaire is its applicability to both the research and the clinical setting, therefore allowing optimal translation of experimental findings to direct patient management.

The only multidimensional questionnaire currently available in Italian language is the Dyspnea 12 questionnaire (D12) (11). It has been shown, in a study conducted on COPD patients, that despite allowing a multidimensional assessment of dyspnea, the D12 and MDP differ in many aspects and measure different sensational characteristics (12). We believe that an Italian version of the MDP would provide an important tool in the research and in the treatment of dyspnea. Aim of this study was therefore to provide a linguistically validated translation of the MDP in Italian.

METHODS

This is a methodological study consisting in a structured translation and linguistic validation of the MDP questionnaire (8) in accordance to the international guidelines. (13, 14) We obtained permission from the copyright holder of the MDP, Dr. Robert B. Banzett, to conduct the project.

Ethics

The study was approved by the local IRB committee (approval number: 704-2018). Patients were informed about the aims and methods of the study. Written informed consent was signed by the all patients for the in-depth interviews.

Translation

The translation and linguistic validation of the questionnaire in Italian required a multistage process (figure), in collaboration with a company specialized in patient-reported outcome measures (Mapi SAS, Language Services Unit, Lyon, France). The multistep process phase was aimed to realize a translation conceptually equivalent to the original version (American English) of the MDP made by using a language easy to understand by the target population.

The MDP was obtained from the developer (8) and forward-translated in Italian by two certified independent translators, native Italian speakers and bilingual in the source language (figure). These translations were discussed and reconciled into a pooled version (version 1), which was reviewed by two native Italian speaking pulmonologists and the local coordinator (GP, pulmonologist) in order to analyze the wording from a clinical perspective. Version 1 was translated back into English by a bilingual nurse. This back-translated version was sent to the developer for comparison with the source instrument. The feedbacks, discussion and amendment from MAPI resulted in a second translated Italian version (version 2) and a report by the local coordinator.

PATIENTS' INTERVIEWS

According to guidelines (13, 14), the questionnaire was tested in individual in-depth, cognitive interviews with 8 Italian patients affected by dyspnea (3 females). Patients were consecutively recruited in the outpatient clinic for respiratory disorders of an Italian NeuroRehabilitation center (Casa di Cura del Policlinico, Milan). Their main conditions were obstructive lung diseases (bronchial asthma in 4 cases, chronic obstructive pulmonary disease in 1 patient), and restrictive lung diseases (amyotrophic lateral sclerosis in 2 cases, one patient affected by primary lateral sclerosis). Aim of the interviews was to test the questionnaire feasibility, clarity, and understandability. The subjects were asked to complete the MDP (version 2) and then to provide general feedback and comments and answer two specific questions. Similarly to Sundh et al. the questions were (15): 1) " What does the instructions / question /response choice mean for you?" with encouragement of the subject to rephrase the item by using other words or to provide examples; 2) "did you have any difficulty understanding the instructions/question/response choice?" with other specific questions in case there were words or phrases difficult to understand and suggested changes of the wording. The interviews took about 1 hour each and were conducted by a pulmonologist (GFSP) and transcribed verbatim. Patients were encouraged to discuss and express their opinion freely about the questions. Given that, the interviews were aimed at testing the understandability results of the interviews these were not coded or presented in themes.

Through inputs of the cognitive interviews, discussion and amendment version 3 was released (see figure). Afterward, a final proofreading and amendment the final linguistic validated translation (final version) was issued.

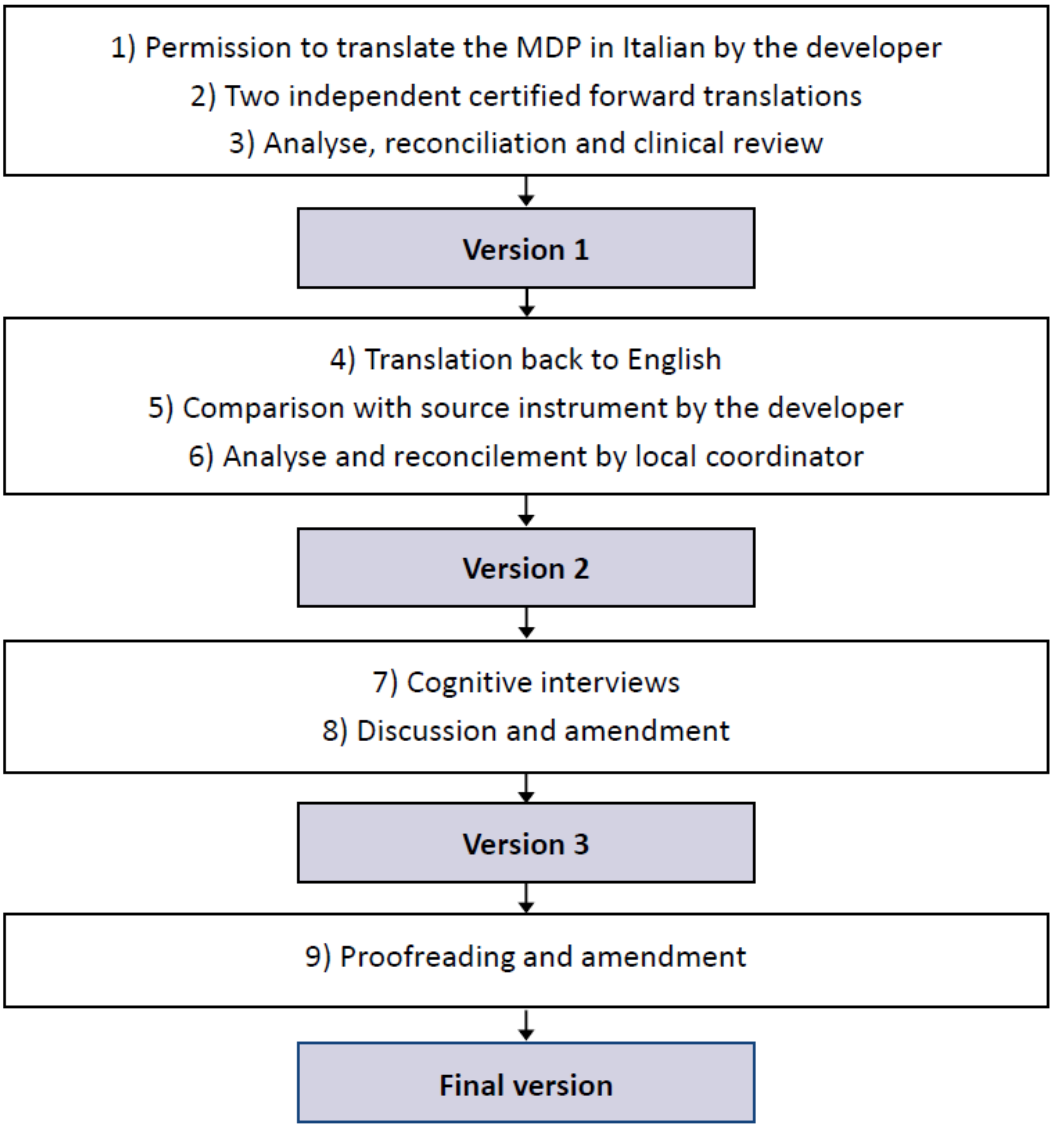

Figure. Flow chart of the translation and linguistic validation study

RESULTS

The final certified copy of the linguistically validated Italian translation of the MDP is published in the Supplementary file for review purpose only. The MDP was completed within a few minutes by all participants. The Italian version has the same layout as the original one. The process of reviewing and the in-depths cognitive interviews resulted in several small linguistic changes to make the instrument conceptually equivalent to the original version.

DISCUSSION

We provided a first linguistically validated version of the MDP in Italian.

As underlined by Sundh and Ekstrom a strength of this type of study is the structured multistage process of translation with several quality check before providing the final version of the questionnaire and in accordance to specific international guidelines (15). Another strength is that the Italian version of the MDP will provide the possibility to compare and pool different populations and countries and foster research on the different dimensions of dyspnea.

As reported by Caruso et al. (11), a study limitation of this type of studies is the nature of bilingual technique translation as bilingual subjects tend to be acculturated to the host culture and could report a different point-of-view from monolingual people (16). However, this limitation should be simply acknowledged. Another study limitation was the small number of clinicians and patients included. However, patients were consecutively recruited and their number was chosen as recommended by the specific international guidelines and with a numerosity similar to previously conducted linguistic validation studies (13, 15). A third study limitation is the lack of psychometric validation of the questionnaire in clinical Italian populations. This step will require further studies.

We believe that standardized symptom rating in a multidimensional fashion, such as the MDP, is at the base of improving patients' care through identifying patient needs and providing better treatments for dyspnea. Therefore, linguistic validation in other languages are required to conduct multinational research

CONCLUSION

This study produced an Italian translation and linguistic validation of the MDP. Further studies should clinically validate the questionnaire in different models of diseases. Final aim of the entire process is to improve dyspnea management by providing a new multidimensional instrument to improve its measurement.

 nome/identificativo_____data e ora

Profilo multidimensionale della dispnea

Testo esplicativo per la prima somministrazione:

L'obiettivo di questo questionario è di aiutarci a comprendere come avverte il suo respiro.
Non vi sono risposte corrette o sbagliate. Vogliamo sapere quello che Lei ci dirà sul Suo respiro.

In questa pagina Le chiediamo quanto spiacevolmente avverte il suo respiro. In una successiva pagina Le chiederemo l'intensità o la forza delle sensazioni legate al suo respiro. La distinzione fra questi due aspetti del respiro potrebbe risultare più chiara se Lei pensasse di ascoltare un suono, ad esempio alla radio. Mentre il volume del suono aumenta, Le potremmo chiedere quanto sia forte o quanto spiacevole sia sentirlo. Ad esempio, una musica che Lei odiasse potrebbe essere fastidiosa anche a basso volume e diventerebbe più fastidiosa all'aumentare del volume; la musica che Le piace non sarebbe fastidiosa, anche ad alto volume.

Scala A1

Utilizzi questa scala per valutare **la sgradevolezza o il disagio** delle Sue sensazioni respiratorie, quanto **difficile da tollerare** sia [era] il suo respiro.

Per favore si focalizzi sul periodo seguente: _____

← ←	0	1	2	3	4	5	6	7	8	9	10
PIACEVOLE	NEUTRO										INSOSTENIBILE

Profilo multidimensionale della dispnea nome/identificativo_____data e ora

Scala A2

Quando il respiro non sembra normale, può avvertire emozioni o "sensazioni". Utilizzando le scale di seguito, per favore ci dica come le sensazione suscitate dal suo respiro la fanno sentire – valuti zero ogni emozione che non ha avvertito.

Per favore si focalizzi sul periodo seguente: _____

	PER NULLA										**MASSIMO IMMAGINABILE**
Depresso/a	0	1	2	3	4	5	6	7	8	9	10
Ansioso/a	0	1	2	3	4	5	6	7	8	9	10
Frustrato/a	0	1	2	3	4	5	6	7	8	9	10
Arrabbiato/a	0	1	2	3	4	5	6	7	8	9	10
Impaurito/a	0	1	2	3	4	5	6	7	8	9	10
Altro?	0	1	2	3	4	5	6	7	8	9	10

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CHAPTER III

MEASURING VITAL CAPACITY IN AMYOTROPHIC LATERAL SCLEROSIS: EFFECTS OF INTERFACES AND REPRODUCIBILITY

ABSTRACT

Background: Deterioration of vital capacity (VC) in amyotrophic lateral sclerosis (ALS) signifies disease progression and indicates need for non-invasive ventilation. Weak facial muscles consequent to ALS, with resulting poor mouth seal, may interfere with the accuracy of VC measurements.

Objectives: To determine whether different interfaces affect VC measurements in ALS patients and whether the interface yielding the largest VC produces an even higher VC when re-measured after one week (learning effect). To explore the relationship between optimal interface VC and sniff nasal pressure (SNIP), a measurement of global inspiratory muscle strength

Methods: Thirty-five patients (17 bulbar and 18 spinal ALS) were studied. Three interfaces (rigid-cylindrical, flanged, oronasal mask) were tested. One week after the first visit, VC was recorded using the optimal interface. SNIP recordings were also obtained.

Results: In the bulbar ALS group, median (interquartile range) VC with the flanged mouthpiece was 8.4% (3.9–15.5) larger than with the cylindrical mouthpiece ($p<0.001$). VC values with oronasal mask were intermediate to VC with the other two interfaces. In spinal ALS, flanged mouthpiece VC was 4.6% (2.3–7.5) larger than with oronasal mask ($p<0.0006$). The latter was 4.5% (0.6–5.2) smaller than with the cylindrical mouthpiece ($p=0.002$). In both groups, VC during the second visit was greater than during the first visit ($p<0.025$). SNIPs were logarithmically related to VC values recorded with the flanged mouthpiece.

Conclusion: A flanged mouthpiece yields the largest values of VC in patients with bulbar and spinal ALS.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is the most frequent of the motor neuron diseases in adults, and is characterized by progressive degeneration of upper and lower motor neurons (1, 2). Degeneration of the motor neurons leads to muscle weakness, including weakness of the respiratory muscles (1, 2). Two-thirds of patients present with limb-onset disease and one-third with bulbar-onset disease (3). Most patients with limb-onset disease eventually develop bulbar symptoms (4). Respiratory failure accounts for 77% of deaths (5).

Respiratory symptoms usually appear late and are related to reductions in vital capacity (VC) (6). Measurements of VC are used to monitor (8, 9) and predict (7) disease progression. VC is also used as a criterion to initiate non-invasive ventilation, to stratify risk for percutaneous endoscopic gastrostomy feeding-tube placement (10), and as a predictor of survival (11, 12). A rigid cylindrical mouthpiece is almost always used as the interface to measure VC in clinical practice. Weak facial muscles consequent to ALS, with resulting poor mouth seal, however, may interfere with the accuracy of VC measurements using a cylindrical mouthpiece. Several additional interfaces such as flanged mouthpieces and oronasal masks can be used to measure VC. These interfaces have not been systematically compared against cylindrical mouthpieces in patients with ALS. Other confounding factors in the accurate measurement of VC include potential learning effect and lack of motivation to perform vigorous respiratory efforts during spirometry secondary to the tenuous psychological condition of these patients (13, 14).

The main objectives of this study were to simultaneously explore for the first time three aspects of VC recording in patients with ALS. First, we sought to determine whether different interfaces affect measurements of VC in ALS patients with and without bulbar dysfunction. Specifically, we expected a flanged mouthpiece would yield greater VC values than a conventional rigid cylindrical mouthpiece and oronasal mask in patients with bulbar dysfunction. Second, we sought to determine whether measurements of VC obtained with the optimal interface (the interface that yielded the largest VC value) would be bigger than baseline values over a one-week period. The third objective was to explore the relationship between VC recorded with the optimal interface and sniff nasal pressure (SNIP) – a global measurement of inspiratory muscle strength.

METHODS

Thirty-five, clinically stable patients with ALS (8) referred to the Pulmonary ALS services of the SS Paolo e Carlo Hospital of the University of Milan, Italy (18 patients) or Hines VAH, Hines, Illinois (17 patients) underwent pulmonary function testing. Patients with acute respiratory failure at the time of presentation, tracheostomy and those unable to perform spirometry were excluded (6, 11). In Milan, analysis of the data collected was carried out after patients signed an informed consent approved by the local Ethics Committee (#466_2018). In Illinois, analysis of the data collected was part of the standard of care and, thus, the Institutional Review Board waived informed consent (#1090568-1).

Neurological evaluation

Before obtaining VC and SNIP recordings, patients underwent neurological evaluation at the ALS clinics of the respective institutions. Functional disability was assessed using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (15). (The ALSFRS-R comprises 12 questions with a maximal score of 48, corresponding to normal functionality in three evaluated domains: bulbar, spinal, respiration.) At the time of data collection, 17 patients had a score of <9 of the bulbar domain in the ALSFRS-R consistent with bulbar impairment (14); this group of patients was designated the bulbar ALS group **(Table 1)**.

Table 1. Patient characteristics			
	Bulbar ALS	Spinal ALS	P
Gender, male/female	16/1	16/2	0.999
Age, years	71.0 (63.0–74.0)	71.0 (61.0–76.5)	0.804
BMI, kg/m^2	22.6 (19.9–26.6)	25.3 (22.6–29.0)	0.077
ALFRS-R, total score	22.0 (15.0–37.0)	30.5 (24.0–41.3)	0.016
ALFRS-R, respiratory score	7.0 (5.0–8.0)	6.5 (4.0–11.3)	0.816
ALFRS-R, bulbar score	5.0 (3.0–7.0)	11.5 (10.0–12.0)	< 0.001
Definition of abbreviations: BMI, body mass index; VC, vital capacity; ALSRS-R, revised amyotrophic lateral sclerosis functional rate scale. Data are median (interquartile range)			

Experiment #1: Measurements of VC using three interfaces

To assess the impact of a rigid cylindrical mouthpiece (Gold Medical Supplies, 100757NW), flanged mouthpiece (Queset Medical, M7700), and oronasal mask (Med Systems, Series 2102) on VC measurements in ALS patients with and without bulbar dysfunction, patients underwent spirometry (Cosmed Quark Spiro, Cosmed in Milan and a TransAir2, Morgan Scientific in Illinois) while seated. Using one interface at a time in random order, patients were instructed to slowly inhale to total lung capacity after a full slow exhalation to residual volume. To limit air entering the mouth from around the rigid cylindrical mouthpiece and with the flanged mouthpiece, one investigator helped the patient keep the mouthpiece in place while gently pressing the patient's lips around the mouthpiece (16). When using the mouthpieces, patients wore nose clips. When using the oronasal mask one investigator pressed the mask tightly against the patient's face to prevent air leaks (17). Patients were verbally encouraged to perform their maximum respiratory effort (12).

Measurements were done according to ATS/ERS guidelines (18). Each patient performed a minimum of three VC maneuvers with a rest period of at least one minute between the maneuvers. If the difference in VC between the largest and next largest maneuver was > 0.150 L, additional trials were undertaken (18). VC values were expressed in liters at body temperature, ambient pressure and gas saturated with water vapor (BTPS) (18) and as percentage predicted according to the Global Lung Function 2012 reference values (19).

Experiment #2: Short term VC reproducibility using optimal interface

To assess the short-term reproducibility of VC recordings, 25 patients agreed to return to the pulmonary function laboratory approximately one week after the first visit. During this second visit, VC was recorded using the optimal interface (interface that yielded the largest VC value on day one).

Experiment #3: SNIP vs VC obtained with optimal interface

The goal of obtaining SNIP recordings was twofold. First, to quantify global inspiratory muscle strength. Second, to explore the relationship between inspiratory muscle strength and VC recorded with the optimal interface.

To record SNIP we inserted a commercially available nasal probe into one of the patient's nostrils and connected it to a portable manometer (MicroRPM Pressure Meter) (20). Patients were studied in the seated position without prior training (21). They were asked to breathe normally with closed mouth and to perform 10 maximal, short, and sharp sniffs from the end of tidal exhalation, each separated by 1 to 2 minutes of resting breathing. No visual feedback was provided (21). The highest value was recorded for analysis. SNIP values were expressed in cm H_2O and as percentage predicted based on the data of Uldry and Fitting (21).

STATISTICAL ANALYSIS

Categorical variables are reported as percentages and continuous variables as medians and interquartile ranges (IQR,s). Comparisons of continuous variables between two subgroups was performed using the Wilcoxon signed-rank test. Fisher exact test was used for categorical variables as appropriate. Friedman's test was used when comparing VC values (liters and percent predicted) recorded with the three interfaces. Spearman's correlation coefficient was used to detect correlation among variables. Multivariate analysis was undertaken to determine which independent variables were associated with the difference in vital capacity (ΔVC) between VC recorded with the optimal interface and the smallest VC recorded with any interface. Variables included in the multivariate analysis had a *p* value less than 0.05 in univariate analysis. Statistical significance was assumed at two-tailed $p<0.05$. All analyses were done using SPSS®23 (IBM SPSS, Armonk, NY).

RESULTS

Patient characteristics

Patient characteristics are summarized in **Table 1**. Most patients were elderly man. Median ALSFRS-R total score for patients with bulbar ALS was 22.0 (15.0–37.0) indicating moderate-severe disease. Median ALSFRS-R total score for patients with spinal ALS was 30.5 (24.0–41.3) indicating mild-moderate disease. As expected, median bulbar ALSFRS-R subscore was worse in patients with bulbar ALS than in patients with spinal ALS ($p<0.001$). Median respiratory ALSFRS-R subscore was 7.0 (5.0–8.0) in patients with bulbar ALS and 6.5 (4.0–11.3) in patients with spinal ALS ($p=0.816$).

Table 2. Vital capacity recorded with three interfaces in 17 patients with bulbar ALS and 18 patients with spinal ALS

	Rigid cylindrical mouthpiece	Flanged mouthpiece	Oronasal mask	P
Bulbar ALS, liters	1.99 (1.35–2.65)	2.44 (1.69–3.03)	2.10 (1.22–2.70)	< 0.0005
Bulbar ALS, percent predicted	52.7 (31.9–68.0)	59.8 (40.4–76.1)	53.7 (34.8–73.8)	< 0.0005
Spinal ALS, liters	2.62 (1.46–4.05)	2.75 (1.44–4.04)	2.34 (1.35–3.89)	0.001
Spinal ALS, percent predicted	72.3 (42.2–94.3)	76.0 (47.4–95.0)	65.1 (41.2–93.7)	0.001

Experiment #1: Measurements of VC using three interfaces

VC results recorded with the three interfaces during the first visit are summarized in **Table 2**. In patients with bulbar ALS and in those with spinal ALS, VC values differed with the three interfaces ($p \leq 0.001$). In patients with bulbar ALS, median VC recorded with the flanged mouthpiece was 380 ml (IQR, 145–570) or 8.4% (IQR, 3.9–15.5) larger than with the rigid tube ($p<0.001$). In these patients, VC values recorded with the oronasal mask were between values recorded with the other two interfaces **(Figure 1, left panel)**.

In patients with spinal ALS, the median VC recorded with the flanged mouthpiece was 185 ml (IQR, 68 - 328) or 4.6% (IQR, 2.3–7.5) larger than with the oronasal mask ($p<0.0006$). The latter, in turn, was 190 ml (IQR, 25–268) or 4.5% (IQR, 0.6–5.2) smaller than with the rigid tube ($p=0.002$). In these patients, VC values recorded with the flanged mouthpiece and rigid tube were not different **(Figure 1, right panel)**.

VC values recorded with the three interfaces in each patient with bulbar ALS and each patient with spinal ALS are shown in **Figure 1**. The maximal difference in VC with the three interfaces was 400 ml (215–710) in patients with bulbar ALS and 245 ml (IQR, 118–343) in patients with spinal ALS ($p=0.013$). The maximal difference in VC expressed as percent predicted in patients with bulbar and spinal ALS were 10.6% (IQR, 6.7–16.1) and 5.5% (IQR, 4.1–7.5) ($p=0.007$).

VCs recorded with the flanged mouthpiece were as large or larger than the VCs recorded with the other two interfaces **(Figure 1)**. In four patients in the bulbar ALS group (patients 2, 9, 15 and 16) and in two patients in the spinal ALS group (patients 6, 17), VCs recorded with the oronasal mask or with the rigid cylindrical mouthpiece were less than 50% predicted while the corresponding values recorded with the flanged mouthpiece were greater than 50% predicted **(Figure 1)**.

On univariate analysis, the difference in vital capacity (ΔVC) between VC recorded with the optimal mouthpiece (flanged mouthpiece) and the smallest VC recorded with any mouthpiece was associated with total and bulbar ALFRS-R scores. (Respiratory ALFRS-R score, SNIP, age, and BMI were not related to ΔVC recorded with different interfaces). On multivariate analysis, bulbar ALFRS-R score on its own was an independent predictor of ΔVC.

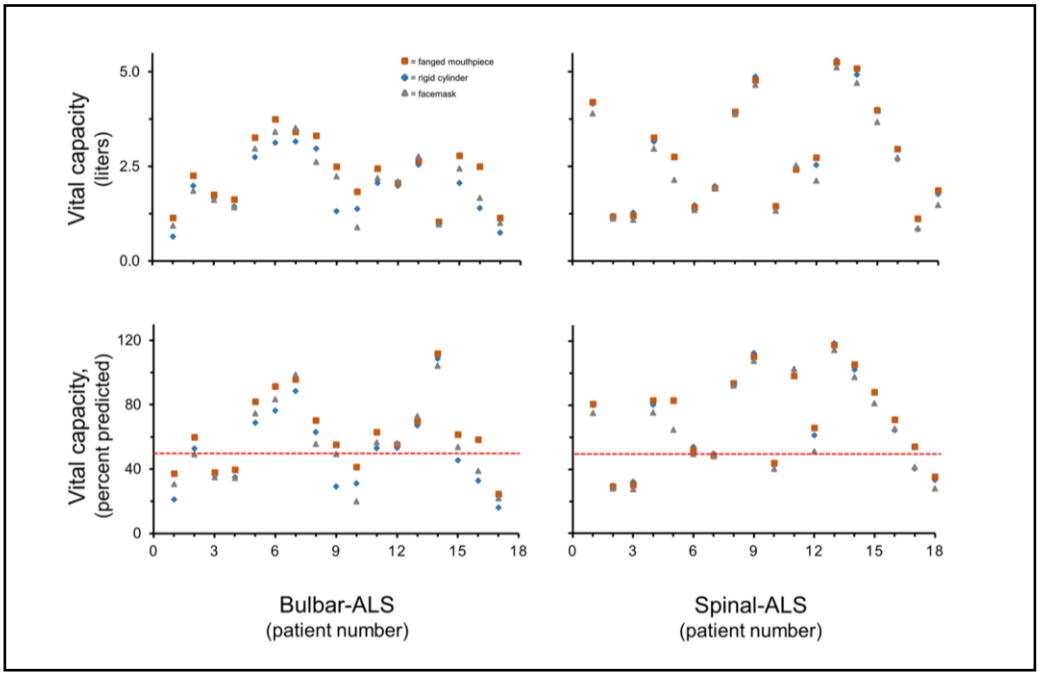

Figure 1. Vital capacity recorded using a flanged mouthpiece *(squares)*, a rigid cylindrical mouthpiece *(diamonds)*, and an oronasal mask *(triangles)* expressed in liters *(upper panels)* and as percent predicted *(lower panels)* in 17 patients with bulbar ALS *(left panels)* and spinal ALS *(right panels)*. The red horizontal line corresponds to 50% predicted vital capacity, a threshold often used to start noninvasive ventilation.

Experiment #2: Short term VC reproducibility using optimal interface

To assess the short-term reproducibility of VC recorded with the flanged mouthpiece (hereafter referred to as optimal interface), 25 patients agreed to return to the laboratory approximately one week after the first visit; 11 of these patients had bulbar ALS and 14 patients had spinal ALS.

In patients with bulbar ALS, the median VC recorded during the second visit was 120 ml (IQR, 50–370) or 3.2% (IQR, 1.2–10.4) greater than the corresponding value recorded during the first visit ($p<0.005$**) (Table 3)**. In patients with spinal ALS, the median VC recorded during the second visit was 85 ml (IQR, 0–180) or 2.1% (IQR, 0–5.7) greater than the corresponding value recorded during the first visit ($p=0.016$) **(Table 3)**. In 5 of 11 (45.5%) patients with bulbar ALS and in 6 of 14 (42.9%) patients with spinal ALS, the VC value measured during the second visit was more than 5% greater than the VC value measured during the first visit.

Table 3. Vital capacity data recorded with the flanged mouthpiece on day 1 and day 7 in in 11 patients with bulbar ALS and 14 patients with spinal ALS

	Day 1	Day 7	P
Bulbar ALS, liters	2.50 (1.75–3.31)	2.55 (2.07–3.79)	0.005
Bulbar ALS, percent predicted	62.9 (39.7–81.9)	65.1 (50.4–89.7)	0.005
Spinal ALS, liters	2.18 (1.37–4.04)	2.41 (1.79–4.04)	0.016
Spinal ALS, percent predicted	60.0 (41.8–90.7)	75.5 (47.0–105.3)	0.016
Data are median (interquartile range)			

Experiment #3: SNIP vs VC obtained with optimal interface

We recorded SNIPs in 10 patients with bulbar ALS and in 11 patients with spinal ALS. The median SNIP in the bulbar group was 34.0 cm H_2O (17.8–61.3) or 35.9% predicted (17.8%–62.9%). The median SINP in the spinal group was 28.0 cm H_2O (19.0–51.0) or 30.0% predicted (20.3%–53.8%). Inspiratory muscle weakness was severe (SNIP<50% predicted) in 7 patients (70%) with bulbar ALS and in 7 patients (64%) with spinal ALS. Inspiratory muscle weakness was moderate (SNIP ranging between 50% and 70% predicted) in 1 patient (10%) with bulbar ALS and in 3 patients (27%) with spinal ALS.

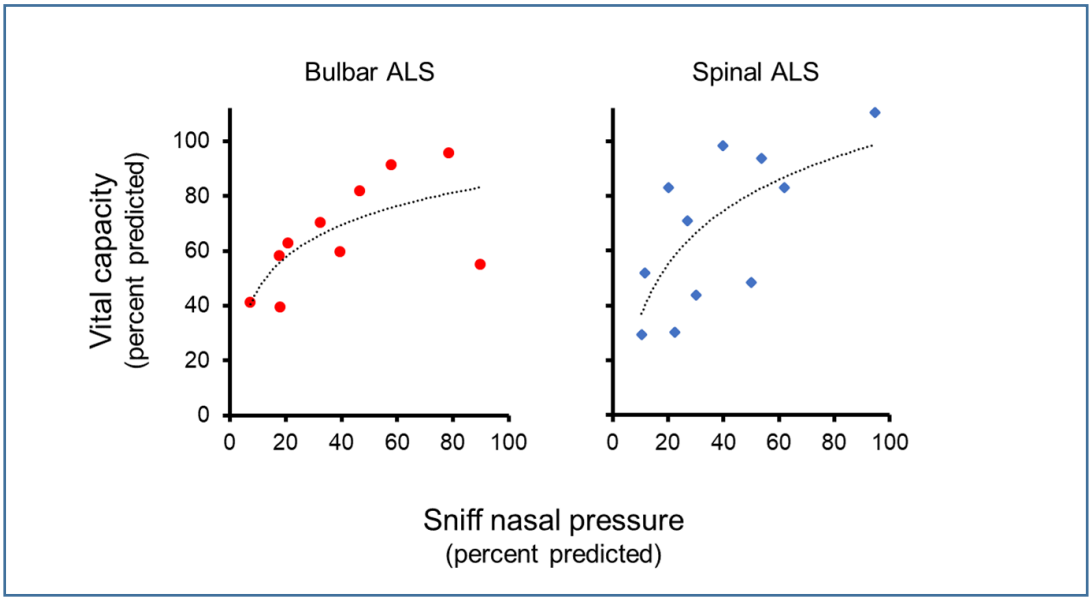

Figure 2. Relationship between vital capacity (percent predicted) and sniff inspiratory pressure (percent predicted) in 10 patients with bulbar ALS (left panel) and 11 patients with spinal ALS (right panel). (see text for details).

Figure 2 presents a plot of SNIP (percent predicted) vs. VC (percent predicted) values in the bulbar ALS group and in the spinal ALS group. The relationship between SNIP and VC appeared curvilinear in both groups **(Figure 2)**. The SNIP-VC relationship was assessed using a log-log relationship (22): the correlation coefficient (r) between SNIP and VC was 0.71 in the bulbar ALS group (p=0.023) and 0.67 in the spinal ALS group (p=0.025). The corresponding coefficients of determination (r^2) were 0.50 and 0.45, respectively

DISCUSSION

This study has three major findings. The flanged mouthpiece yielded the largest recordings of VC in patients with bulbar and spinal ALS. After a period of approximately one week, most patients with bulbar and spinal ALS achieved larger VC recordings than at baseline. SNIPs were logarithmically related to VC values recorded with the flanged mouthpiece.

Inter-interface comparisons

Several factors modulate the volume of air inhaled during a VC maneuver. These include patient cooperation (12, 23), respiratory muscle strength (24), glottic patency (6), and proper interface seal (17). In patients with bulbar ALS, the use of a flanged mouthpiece yielded larger VC recordings than with the conventional rigid cylinder. This was true despite the operator attempt to limit air entering the mouth from around the mouthpiece by gently pressing the patient's lips around the mouthpiece itself (16). The median difference in VC recordings between the flanged and the conventional rigid cylinder was large enough that selected patients would have been misclassified as requiring non-invasive ventilation or assigned an incorrectly elevated risk level for percutaneous endoscopic gastrostomy feeding-tube placement **(Figure 1)**.

In patients with spinal ALS, VC values recorded with the flanged mouthpiece and rigid tube were equivalent. In both groups of patients, the oronasal mask yielded the smallest VC values. This finding extends observations of Wohlgemuth et al (17) who compared VC recorded with a flanged mouthpiece and with an oronasal mask in 22 healthy subjects (no rigid cylinder was tested by the investigators). In that study, VC measured with the oronasal mask was 200 mL smaller than the corresponding value recorded with the flanged mouthpiece (17). One mechanism that could contribute to this result is an unnoticed flow of air around the oronasal mask. This is unlikely because in both the study of Wohlgemuth et al (17) and in the present study investigators pressed the mask tightly against the patient's face. No participant in either study had a beard which could have precluded a proper sealing of the mask against the face (17). Other mechanisms for the smaller VC with the oronasal mask include submaximal effort (consequent to tight pressure against the face) and relative fixation of the head (17). When using the flanged mouthpiece, one investigator gently held the lips around the mouthpiece to prevent flow of air around the interface. When using a similar technique in healthy subjects, Fiz et al (16) reported that maximal expiratory pressures were greater when the investigator

applied manual compression on the lips of study participants than when the investigator did not apply compression.

Short term VC reproducibility using optimal interface

When recordings of VC using the optimal interface were repeated after one week, VC was 3.2% greater in the bulbar ALS group and 2.1% greater in the spinal ALS group. These values are within the 1.8%-3.5% within-subject coefficient of variation of VC recorded in healthy subjects retested over a period of 1-35 days (17, 25). In more than 40% of patients with bulbar or spinal ALS, the difference in VC was greater than 5%. That is, when performing VC maneuvers, some patients with ALS exhibit a learning effect–operationally defined as a within-subject increase in VC greater than 5%. This learning effect is larger than the within-subject coefficient of variation of VC reported in healthy subjects (17, 25). Consequently, whenever clinical decisions are being taken based on borderline low values of VC, a second testing should be performed within a week in order to ensure that a low VC value signifies true respiratory muscle weakness rather than submaximal efforts (see below).

SNIP vs VC obtained with optimal interface

SNIP values recorded in patients with bulbar ALS were not different from those recorded in patients with spinal ALS. This is an unexpected result considering that difficulty in sealing the mouth, upper airway collapse and discoordinated contractions should produce smaller SNIPs in patients with bulbar than with spinal ALS (26).

In most patients with bulbar and spinal ALS, VC recorded with the optimal interface was well preserved when SNIP pressures were greater than 40% predicted; when SNIP pressures were less than 40% predicted, in several patients there was an abrupt decline in VC **(Figure 2)**. This partial discrepancy between respiratory muscle weakness and VC in patients with either ALS (6, 24, 26) or other neuromuscular disorders (22, 24) likely results from the shape of the relaxation pressure-volume curve of the respiratory system, which becomes curvilinear only

near the extremes of the VC (23). A decrease in respiratory strength to 50% of normal reduces VC by only 15%, whereas further muscle weakness produces a much greater reduction in VC (22). An additional factor that could contribute to the partial discrepancy between the reduction of SNIP and VC could be a greater impairment of the inspiratory muscles than of the expiratory muscles (6). Without measurement of expiratory muscle function, this remains speculative.

The SNIP-VC relationship was characterized by a wide range of VC values in patients with similar degrees of respiratory muscle weakness both in the bulbar and spinal groups **(Figure 2)**. Mechanisms responsible for this finding (24, 26), include patient comprehension and cooperation with the maneuvers, differences in respiratory mechanics, and differences in the distribution of muscle weakness (27).

Critique of methods/Limitations

The total number of participants in the study was relatively small. On performing a post-hoc sample size calculation, we determined that a sample size of 10 patients provides 83% power at an α level of 0.05. This signifies that our sample sizes of 17 patients for the bulbar group and 18 patients for the spinal group were sufficient to capture differences in VC for the three types of interface. Two teams of investigators used two different spirometers—one in Italy and one in the US. We reason that this was not a significant drawback for several reasons. The two teams closely coordinated and planned the investigation–including sharing step-by-step instructions on how to perform spirometry. The Italian team visited the US team to ensure uniformity of data acquisition. This approach has been successful used to avoid systematic operator and device errors (25)

CLINICAL IMPLICATIONS

Respiratory muscle weakness is an obligatory component of ALS (6). Monitoring VC in patients with ALS affords critical information on disease progression (8, 9), risk stratification (10) and mortality (11, 12). To most accurately record VC we recommend against the use of conventional cylindrical mouthpieces and suggest the routine use of flanged mouthpiece in all

patients with ALS–whether they have bulbar or spinal ALS. Unlike Wohlgemuth et al (17), we do not recommend use of an oronasal mask in patients with ALS. When VC results are borderline, we recommend repeating VC recordings after about one week to overcome the learning effect. Even when using an optimal interface, SNIP measurements can be of value in detecting respiratory muscle involvement at an early stage of ALS–when VC is still well preserved (26).

In conclusion, the flanged mouthpiece yields the largest values of VC in patients with bulbar and spinal ALS.

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CHAPTER IV

EFFECTS OF AIR STACKING ON DYSPNEA AND LUNG FUNCTION IN NEUROMUSCULAR DISEASES

ABSTRACT

Objective: To investigate whether the decrease in dyspnea in neuromuscular diseases after air stacking (AS) occurs mostly in patients with decreased inspiratory muscles force and ensuing chest wall restriction or heterogeneous ventilation across the lungs.

Design: interventional, before-after study.

Setting: a neurorehabilitation, inpatient and outpatient center.

Participants: 15 consecutive adult patients affected by neuromuscular diseases.

Intervention: AS treatment.

Main Outcome Measures: subjects had vital capacity (VC) and sniff nasal inspiratory pressure (SNIP) measured. Borg score, oxygen saturation and ventilation heterogeneity across the lung as estimated from the difference between respiratory resistance at 5 and 19 Hz (R5-19) with the forced oscillation technique were measured before and 5, 30, 60, and 120 min after applying AS.

Results: Before AS, Borg score was significantly related to R5-19 (r2 0.46, $p< 0.05$), but not to VC % pred, SNIP % pred, and time since symptom onset. After AS, average Borg score gradually decreased ($p=0.005$), whereas R5, R5-19 , and X5 tended to improve, despite not reaching statistical significance. The decrease in dyspnea at 60 and 120 min after AS significantly correlated with baseline R5-19 (r2 0.49, $p< 0.01$ and r2 0.29, $p< 0.05$, respectively), but not with VC % pred, SNIP % pred, time since symptom onset, and clinical severity score for patients affected by amyotrophic lateral sclerosis.

Conclusion: these findings suggest that dyspnea in neuromuscular diseases is related to heterogeneous ventilation rather than inspiratory muscle force and/or lung volumes decrease. Restoring ventilation distribution across the lungs with AS appears to improve dyspnea.

Abbreviations: ALS = amyotrophic lateral sclerosis; AS = air stacking; FOT = forced oscillation technique; SpO2 = oxygen saturation index; SNIP = sniff nasal inspiratory pressure; VC = vital capacity; R5 = inspiratory flow resistance at 5 Hz; R19 = inspiratory flow resistance at 19 Hz; R5-19 = difference in respiratory resistance between 5 and 19 Hz; X5 = inspiratory reactance at 5 Hz.

INTRODUCTION

Impairment of the respiratory muscles function in amyotrophic lateral sclerosis (ALS), myopathies, or spinal cord injuries leads to lung volume reduction, hypoventilation, accumulation of secretions within the bronchial and alveolar compartments, and finally to dyspnea and reduced quality of life. (1,2) Physiotherapy programs that help temporarily expand the chest wall such as air stacking (AS) (3) are of clinical benefit in these disease conditions as they help reduce cough and increase expectoration.4 Presumably, this is achieved by restoring lung expansion to a volume higher than that reduced by the primary disease, thus increasing lung elastic recoil and the expiratory force necessary to clear the bronchial secretions. (5,6)

In a recent internal survey we observed that many patients affected by neuromuscular diseases reported a significant improvement of dyspnea of some duration soon after performing the AS exercise, whereas others did not. According to current opinion, with the worsening of the neuromuscular disease, dyspnea increases as a result of a decrease in inspiratory muscles force below the threshold necessary to maintain normal chest wall expansion during breathing. (2) Yet, under these conditions, ventilation loses its normal homogeneous distribution across the lung, a fact that could contribute to increase dyspnea through the stimulation of the neuroreceptors located within the lung and respiratory tract. Two previous studies documented indeed that lung compliance was reduced in ALS and significantly increased after a series of deep breaths. (7,8) This is consistent with ventilation shifting from heterogeneous to more homogeneous conditions with the deep breath (9), thus possibly contributing to explain the decrease in dyspnea we observed in some patients after applying the AS.

On this ground, we reasoned that if it is the decrease in muscle force and lung volumes the main cause of dyspnea with the neurological disease, then the effects of AS on dyspnea should be larger in the patients with lower vital capacity (VC) and/or inspiratory muscles force. If in contrast, it is the presence of microatelectases formation what occurs with neuromuscular diseases thus making ventilation patchy, then the resulting increase of dyspnea would be blunted by the AS technique in the patients with more heterogeneous ventilation. This hypothesis was tested in a group of 15 patients affected by neuromuscular diseases by measuring spirometry, respiratory muscles force and ventilation distribution with the newly developed forced oscillation technique (FOT). The latter was measured before and 5, 30, 60,

and 120 min after applying the AS. Heterogeneous distribution of ventilation was estimated from the difference in respiratory resistance at 5 and 19 Hz (R5-19). (9-17)

MATERIALS AND METHODS

Subjects

Fifteen patients with neuromuscular diseases were included in the protocol. Nine of them were affected by ALS, (1) 2 by spinal muscular atrophy type 2, 1 by multisystemic atrophy type c, 1 by primary lateral sclerosis, 1 by myasthenia gravis, and 1 by primary carnitine deficiency. To be included in the study they had to be in stable clinical conditions, free from other neurological, cardiovascular, and respiratory diseases, and infectious exacerbations over the previous four weeks, and willing to cooperate. Exclusion criteria were clinical evidence of bulbar dysfunction affecting speech and swallowing musculature capable of blunting the benefits of the AS and/or altering the lung function measurements, and non-invasive ventilation treatment.

The study protocol was approved by the local Ethics Committee and written informed consent was obtained from each subject before entering the study. Main anthropometric, clinical and neurological functional parameters are presented in Table 1.

Lung function measurements

Spirometry and slow vital capacity (VC) were measured with a Quark Spiro spirometer (Cosmed, Rome, Italy) according to the current guidelines. (18) Specifically, VC was measured during a fast maximal inspiratory maneuver taken after a slow expiration from end-tidal inspiration to residual volume. The test was terminated when within and between maneuvers criteria were achieved. The largest VC value of three acceptable maneuvers was retained. (18) Predicted values for spirometry and lung volumes were from Quanjer et al. (19)

Sniff nasal inspiratory pressure (SNIP) was measured with a MicroRPM Pressure Meter (MD Spiro, Lewiston, ME). After choosing the nasal probe that best fit the nostril with no leaks around it, pressure was measured during sniffing maneuvers initiated from the end of tidal expiration and with the maximal effort. The maneuver was repeated 10 times in each patient

with time intervals between the maneuvers of about 1-2 min. The highest value was retained for statistical analysis. Predicted values are from Morgan et al. (20)

Respiratory impedance was measured at the mouth during tidal breathing for 2 minutes by a commercial FOT system (Resmon Pro, Restech, Milan, Italy) according to the current guidelines.14 The patients were comfortably seated on an armchair, wearing a nose clip, with an operator supporting their cheeks and floor of the mouth with both hands. The device generates simultaneous sinusoidal pressure oscillations at 5, 11, and 19 Hz frequency, and of ~ 2 cmH2O amplitude applied at the mouth through a mouthpiece. Artifacts due to glottis closure, cough and expiratory flow limitation were automatically discarded by the device. (21) The analysis of the data was conducted on at least 10 regular breaths necessary to compute the inspiratory flow resistance at 5 and 19 Hz (R5 and R19, respectively) and inspiratory reactance at 5 Hz (X5). The difference between R5 and R19 (R5-19) was taken as an index of serial and parallel ventilation heterogeneities. (9-17) Oxygen saturation (SpO2) was measured by a pulsoximeter.

Symptom assessment

Dyspnea was estimated with the help of a modified Borg scale. Special care was taken in the pre-study day to make sure that the subjects were fully informed of the aim of the study and familiarized with the Borg score so that they could properly rate the intensity of dyspnea.

The time since dyspnea occurred with the disease for each patient was calculated in months.

The amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) was used to estimate the severity of the disease in the ALS patients. (1)

PROTOCOL

On a pre-study day, the patients attended the laboratory for medical history and neurological clinical examination including measurements of blood pressure, heart rate, and simple spirometry. Then SNIP and VC were measured with a flanged mouthpiece as described above in the lung function measurements session. The patients familiarized with the AS technique with the help of a physiotherapist according to the standard methodology. (22) Finally, they familiarized with the FOT technique until repeatable results were achieved.

On the study day, the FOT was measured in duplicate during 2 min of tidal breathing, and soon after Borg score and SaO2. Then, AS was delivered according to Kang and Bach. (22) Briefly, the patients were requested to take a deep breath and hold their breath, immediately after which air was manually insufflated through a mask. Three sets of maneuvers were repeated interspersed with tidal breathing. FOT, Borg score and SaO2 were measured 5, 30, 60 and 120 min after AS.

STATISTICAL ANALYSIS

Differences in Borg score, SaO2, R5, R5-19, and X5 between conditions were tested for statistical significance by the one-way ANOVA test corrected with Bonferroni test and Holm-Sidak post-hoc test whenever $p<0.05$. All values are expressed as mean±SD. The sample size calculation was performed before the study. At least 15 subjects were required for a power of 0.95 to obtain a correlation coefficient of at least 0.51 between dyspnea and R5-19 at baseline and the decrease in dyspnea after AS and baseline R5-19. The choice of the coefficient correlation for the study was based on two studies examining the relationship between symptoms and lung function in asthmatic patients. (23,24)

RESULTS

The clinical neurological conditions well represent the categories of patients with neurological disease for whom AS is indicated. (22)

Patient number	15
Sex, m/f	11/4
Age, yr	60±19
Smoking habit, current/former/never	2/1/12
Height, cm	168±8
BMI, $Kg \cdot m^{-2}$	25±4
VC, L (% of predicted)	2.20±0.97 (61±24)
SNIP, cm H_2O (% predicted)	46±28 (47±27)
ALSFRS-R	30±9
Time since dyspnea onset before the study, months	16±15

Table 1. Main anthropometric and neurological and lung function parameters. Legend: BMI, body mass index; VC, vital capacity; SNIP, sniff nasal inspiratory pressure; ALSFRS-R, amyotrophic lateral sclerosis functional rating scale revised. Data are mean ± SD.

At baseline conditions, Borg score was significantly related to R5-19 (r2 0.46, $p< 0.05$) (figure 1), but not to VC % pred (r2 0.01, NS), SNIP % pred (r2 0.01, NS), and time since dyspnea onset (r2 0.04, NS).

After AS, average Borg score gradually decreased ($p=0.005$); no significant differences were observed between baseline and different time points with the Holm-Sidak post-hoc test. R5, R5-19 , and X5 tended to decrease though this was not statistically significant, whereas SaO2 remained stable. The main results are reported in Table 2.

	Baseline	5’	30’	60’	120’	p-value
Borg score, units	1.8±1.5	1.4±1.2	1.30±1.1	1.2±1.0	1.3±1.0	0.005
SaO_2, %	96.5±1.7	97.1±1.6	96.9±1.6	96.7±1.4	96.5±1.5	1.055
R_5, cm H_2O/L/s	3.11±1.21	2.77±1.02	2.86±0.98	2.79±1.18	2.63±0.87	0.275
R_{5-19}, cm H_2O/L/s	0.54±0.82	0.38±0.83	0.28±0.80	0.31±0.64	0.24±0.57	0.080
X_5, cm H_2O/L/s	-1.06±0.74	-0.88±0.59	-0.91±0.64	-0.80±0.58	-0.80±0.46	0.055

Table 2. Clinical and main FOT parameters before and 5, 30, 60, ad 120 min after the AS maneuvers.

Legend: R_5 and R_{5-19}, difference between respiratory resistance at 5 and 19 Hz; X_5, respiratory reactance at 5 Hz. Statistical analysis was conducted with analysis of variance (ANOVA) for repeated measures with Bonferroni correction.

The decrease of Borg score at 60 and 120 min after AS negatively correlated with baseline R5-19 (r2 0.49, $p< 0.01$ and r2 0.29, $p< 0.05$, respectively) (figures 2 and 3). No significant relationships were observed between the decrease of Borg score at any time after applying the AS and VC or SNIP as % predicted, or time since dyspnea onset. This suggests that dyspnea decreased after AS more in the patients with larger heterogeneous ventilation at baseline. Visual analysis of figures 1-3 does not reveal any specific pattern distribution of the different neuromuscular conditions contributing to the relationship between symptoms and lung function. In the subgroup of the ALS patients the decrease of Borg score after applying the AS never correlated with the ALSFRS-R.

No relationships were observed between any of the following parameters, i.e., R5-19 at baseline, SNIP % pred, and VC % pred.

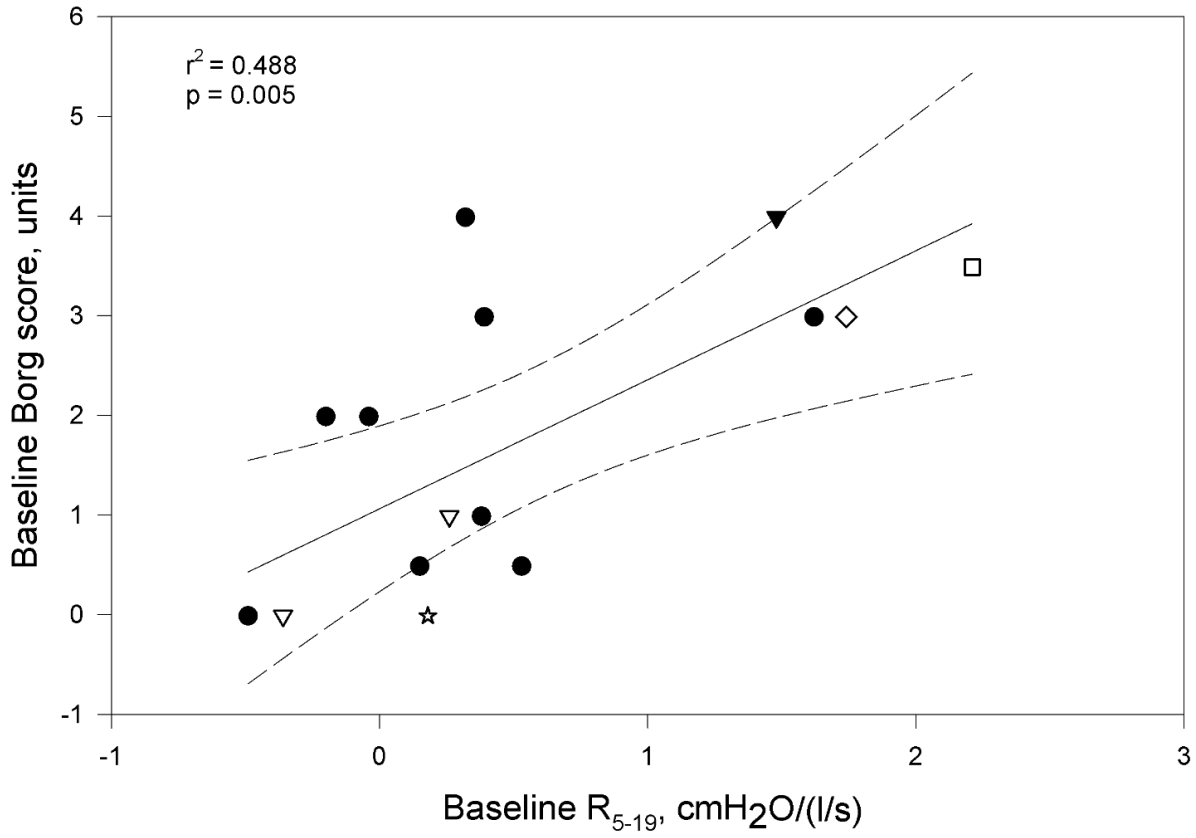

Figure 1. Relationship between baseline Borg score and R5-19. Symbols identify the patients affected by ALS (full circles), spinal muscular atrophy type 2 (full triangles), multisystemic atrophy type c (empty triangle), primary lateral sclerosis (diamond), myasthenia gravis (square), and primary carnitine deficiency (star).

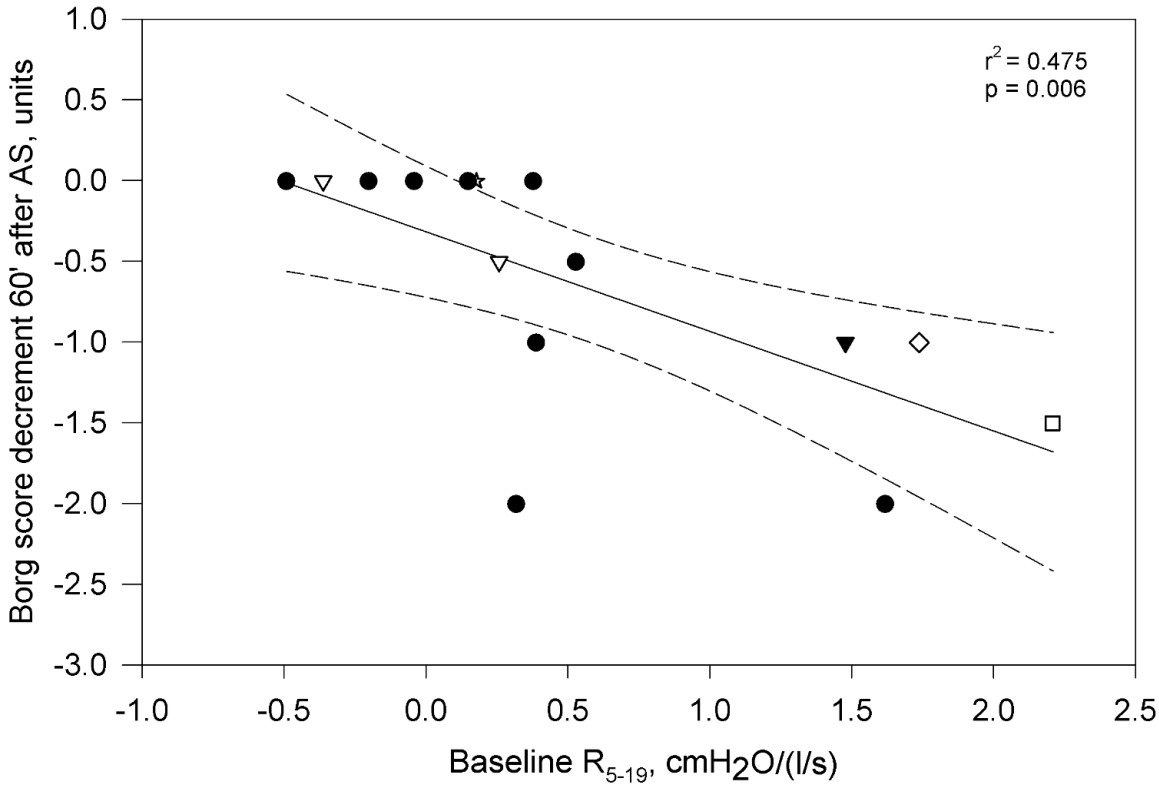

Figure 2. Relationship between the decrease of Borg score 60 min after applying AS and baseline R5-19. Symbols as in figure 1.

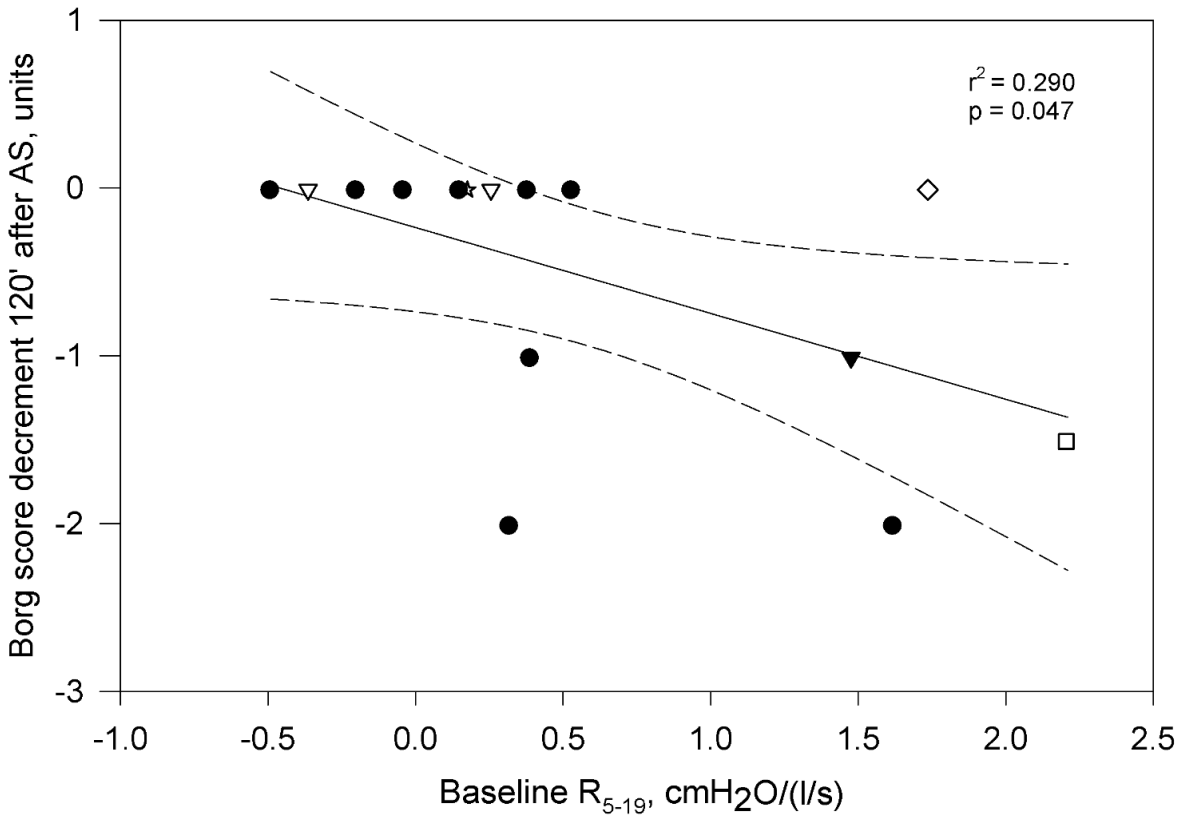

Figure 3. Relationship between the decrease of Borg score 120 min after applying AS and baseline R5-19. Symbols as in figure 1.

DISCUSSION

The main results of this study are that in neuromuscular patients dyspnea at baseline conditions significantly correlated with heterogeneous ventilation but not with VC % pred or SNIP % pred. After applying the AS the decrease in dyspnea significantly correlated with the degree of baseline heterogeneous ventilation and not with VC % pred or SNIP % pred. Taken together, these findings suggest that dyspnea in the neuromuscular diseases is presumably linked to the presence of patchy ventilation.

Comments on methodology

Ventilation distribution was assessed with the FOT rather than standard pulmonary function tests such as spirometry. This is because maximum flow is not or little sensitive to heterogeneous distribution of the disease across the lungs.25 The FOT may provide indeed, a great deal of information on ventilation independently of the underlying functional and clinical conditions.9-13,15-17 The basic concept is that in case of parallel or in series ventilation heterogeneities low frequency oscillations may travel through the lung regions where flow is somewhat hampered either because of intrinsic airway narrowing or decrease in tethering external pressure, thus contributing to detect the increased resistance. In contrast, high frequency oscillations are diverted to the well ventilated regions where air flow resistance is low or the alveolar units are well open. As a result, a high difference in respiratory resistance between low and high frequency oscillations (R5-19) indicates the presence of heterogenous ventilation.12,15-17,26,27 A second advantage of the FOT is that the technique allows exploring the mechanisms of dyspnea within the same lung tidal volume where the symptom is perceived. This would not have been possible with spirometry due to the high lung volume at which function is examined.

INTERPRETATION OF RESULTS

Ventilation heterogeneity was the only functional feature significantly related to baseline dyspnea and its decrease after applying AS until the end of the study in our neuromuscular patients. This suggests that anomalous distribution of ventilation within the lungs is presumably one of the mechanical determinants of dyspnea in neuromuscular diseases and both may improve with the AS technique.

Dyspnea is triggered by the stimulation of the irritant receptors and bronchial C fibers with the neural impulses being conveyed to the central nervous system via vagus nerve independently of the underlying respiratory disease. (28) It is also well known that the irritant receptors within the peripheral airways are sensitive to the size of the airways and most of all flow within the airways. (29) On this physiological ground, we try to interpret the findings of the present study as follows. When the decrease in the operational lung volumes and breathing in neuromuscular diseases exceeds a given threshold as a result of the reduced respiratory muscle force, some lung regions will become gradually hypoventilated due to a decrease in local lung elastic pressure. This will force ventilation to shift from poorly to better ventilated regions in order to maintain gas exchange still or near normal. With this extra gas volume and flow within these lung regions the irritant receptors will then increase their impulse frequency to the central nervous system to signal the presence of anomalous ventilation condition. That this may be so in our patients is sustained by the observation that higher Borg scores were observed at baseline in the patients with higher R5-19. With the increase in lung expansion and ensuing lung elastic recoil with AS, ventilation became more homogeneous but only in the patients with elevated R5-19 with flow being now redistributed to the previously hypoventilated regions. As a result, dyspnea could decrease presumably because of the reduced number of stimuli arising from the irritant receptors no more exposed to hyperventilation. The decrease in dyspnea with the improvement of ventilation tended to initiate about 30 min after AS but then remained significant until the end of the two-hour observation period, thus suggesting a long-lasting effect of the AS treatment.

The lack of any relationship between the decrease in dyspnea after AS and VC or SNIP as % predicted may be explained by the complexity of the respiratory involvement in the neuromuscular diseases. As far as we know, VC is a bidimensional parameter with the two extremes being set by different mechanisms. (30) If the upper extreme depends on the force

exerted by the inspiratory muscles and necessary to fully extend the chest wall and lung, the lower one is determined by the force of the expiratory muscles unless airway closure occurs prematurely. SNIP in contrast is determined by the force generated by the inspiratory muscles at the end of tidal expiration.30 This explains why VC and SNIP are poorly interrelated because of their different mechanical determinants. Yet they both decrease over time indicating the progression of the disease and the need to assist ventilation. We suspect that the main reason for them to be unrelated to dyspnea is that the main site where the symptom originates is within lung regions that bear the ventilation out of the adjacent hypoventilated areas as above mentioned. The lack of any relationship between dyspnea or its decrease after AS and time since dyspnea occurred with the disease or the ALSFRS-R in the ALS patients presumably reflects the complexity of the disease where adaptation to dyspnea over time or additional factors may interfere with the interpretation of the findings.

STUDY LIMITATIONS

We acknowledge some limitations of our study. First, the comparative analysis of dyspnea and lung function might be disturbed by the different intrinsic nature of these variables, i.e., subjective vs. objective. Well aware of this problem we dedicated much time before the study to teach our patients how to perceive and score the symptom. Second, the relationship between symptoms and lung function was examined by regression analysis even though we well know that this may suggest but not prove any causal relationship between the variables. As a matter of fact, visual analysis of the data shows some clumps of data that could be captured by different statistical ways. Yet we justify our statistical approach on the ground that linear regression analysis has already been repeatedly used in previous studies (23,24) and that notwithstanding the low sample size, the statistical outcome of the present study was achieved. Third, selection of the subjects was limited to well cooperative patients who intended to fully complete the study with great commitment. It is premature to extend the results of our study to all patients in whom AS is indicated.

CONCLUSIONS

To our knowledge, this is the first study suggesting that dyspnea in neuromuscular diseases might be linked to heterogeneous ventilation and improve with AS as a result of a more homogeneous ventilation. If replicated in further studies, these results may have important clinical impact in the field of the neuromuscular diseases. First, they substantiate the effects of AS on dyspnea of the patients. In this sense AS assumes a critical role in these diseases for the patients who feel short of breath. Second, even if we did not measure the duration of the clinical and functional effects of AS, these data would suggest that the benefits are quite long lasting. Further studies may be however, necessary to examine the duration of the clinical benefits after applying the AS in order to set the best daily frequency of the respiratory training. Third, AS appears to be of no benefit for the patients in whom the respiratory conditions are still preserved. In this context, measurement of pulmonary impedance by FOT may be a simple tool for the proper clinical indications to AS. Future studies will be necessary to substantiate and expand the present findings to best improve our clinical approach to modulate dyspnea in patients with neuromuscular diseases.

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