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REVIEW

Respiratory muscle involvement in multiple sclerosis

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ABSTRACT: Respiratory complications are common in the terminal stages of multiple sclerosis and contribute to mortality in these patients. When respiratory motor pathways are involved, respiratory muscle weakness frequently occurs. Although it is well established that weakness of the respiratory muscles produces a restrictive ventilatory defect, the degree of muscle weakness and pulmonary function are poorly related. Respiratory muscle weakness was observed in patients with normal or near normal pulmonary function. Expiratory muscle weakness is more prominent than inspiratory muscle weakness and may impair performance of coughing. Subsequently, in addition to bulbar dysfunction, respiratory muscle weakness may contribute to ineffective coughing, pneumonia, and sometimes even acute ventilatory failure may ensue. Respiratory muscle weakness may also occur early in the course of the disease. Recent studies suggest that the respiratory muscles can be trained for both strength and endurance in multiple sclerosis patients. Whether respiratory muscle training delays the development of respiratory dysfunction and subsequently improves exercise capacity and cough efficacy, prevents pulmonary complications or prolongs survival in the long-term remains to be determined.

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Multiple sclerosis (MS) is a primary disorder of the central nervous system. Its pathological hallmark is the presence of multiple areas of nerve demyelination which may vary in size and location. Hence, disturbances of nerve conduction may be responsible for the symptoms that typically develop acutely, remain stable for a few weeks, and then partially regress. MS affects motor pathways and causes muscle weakness and spasticity. Although much of the interest was devoted to upper and lower limb muscles involved in activities of daily living and ambulation, recent papers have also addressed the issue of respiratory muscle weakness in these patients [1–4].

The diagnosis of MS frequently prompts the question of whether or not the disease will be fatal [5–7]. Most studies on mortality focus on mortality patterns and rates rather than the actual cause of death. The studies addressing the causes of death were based on selective populations or focus on specific causes of death such as neoplasms [8–11]. However, several studies have indicated that approximately half of the patients died from complications of MS, with pneumonia being the most frequent underlying cause [12–14]. These data were based on a MS population followed prospectively up to 16 yrs, and were likely more accurate than those from death certificates.

Since pulmonary complications make an important contribution to morbidity and mortality in MS, it is useful to review pulmonary function and respiratory muscle function in MS. In addition, strategies to improve respiratory muscle function may be important to reduce the deterioration of pulmonary function and perhaps improve symptoms and survival.

Pulmonary symptoms and morbidity

When respiratory motor pathways are involved, respiratory muscle impairment and subsequent acute or chronic ventilatory failure may ensue. As in other neuromuscular diseases [15–17], respiratory muscle weakness, abnormal control of breathing, or increased respiratory system elastance with increased work of breathing may be involved in the respiratory disturbances in MS.

The largest series of MS patients with respiratory involvement was reported by HOWARD *et al.* [18], who studied 19 cases of respiratory complications developing, on average 9.5 yrs after the onset of neurological symptoms. Overall, high cervical cord lesions were seen in 17 of 19 patients and bulbar lesions in 12 of 19 patients presenting with acute respiratory insufficiency. The authors divided the causes of respiratory dysfunction into five categories: respiratory muscle weakness, bulbar dysfunction, obstructive sleep apnoea, abnormalities of respiratory control, and paroxysmal hyperventilation (table 1). In most cases, more than one cause was found. Bulbar dysfunction increased the risk of aspiration and lower respiratory tract infection. In their review, CARTER and NOSEWORTHY [19] frequently observed progressive breathlessness, orthopnoea, and sleep disturbances as signs of impending respiratory failure. Patients with significant diaphragm weakness

Table 1. – Patterns of respiratory involvement in multiple sclerosis

Type of respiratory involvement	Number of patients (n=19)
Respiratory muscle weakness	14
Bulbar dysfunction	9
Obstructive sleep apnoea	1
Abnormalities of respiratory control	6
Paroxysmal hyperventilation	3

Data from [18, 19].

had prominent orthopnoea and sleep disturbance, because of the drop in vital capacity when assuming the supine position [20].

Two patterns of respiratory dysfunction may occur in MS [1]. Firstly, acute respiratory failure might develop secondary to demyelinating lesions of the cervical spinal cord or the respiratory centres of the medulla. Secondly, aspiration, pneumonia, and respiratory failure may occur in advanced stages of the disease.

Acute respiratory insufficiency has been described in MS patients [18, 19, 21–26], but is relatively rare in MS. Other investigations have stated that acute, occasionally fatal, respiratory failure is not uncommon [12, 27]. Acute respiratory failure usually reflects extensive bulbar disease. The consequences of large lesions of the medulla or cervical spinal cord include altered ventilatory patterns, acute loss of voluntary control of respiration, and apnoea causing acute respiratory failure. However, the detailed analysis of acute respiratory involvement in MS is often complicated by secondary systemic factors such as dehydration, aspiration pneumonitis and sepsis [20]. Ventilatory support may be required during an acute episode [22, 26, 28].

The second pattern of respiratory dysfunction is characterized by atelectasis, aspiration, and pneumonia; these are common terminal events in the advanced stages of MS. In addition, aspiration pneumonia and atelectasis are frequently the precipitating causes of hospitalization in severe disease [27, 28].

Respiratory involvement may occur earlier in the course of the disease, particularly during relapses [29], but the degree of pulmonary dysfunction in the milder stages of MS is not well characterized. For early diagnosis of respiratory symptoms, SMELTZER *et al.* [1] developed the Pulmonary Index (table 2), comprised of four clinical signs: 1) the patient's report of difficulty in clearing pulmonary secretions; 2) the patient's report of a weakened cough; 3) the examiner's observation of the patient's cough; and 4) the ability to count on a single exhalation. Of 25 patients, only eight reported that their cough was weak, whereas an examiner rated the cough of 15 patients as weak. Eleven patients reported difficulty clearing pulmonary secretions and occasional choking. Eight were unable to count to 20 on a single exhalation. Expiratory muscle weakness was significantly related to the Pulmonary Index ($r=0.70$, $p<0.001$). Other studies confirmed the importance of expiratory muscle weakness in cough efficacy in neuromuscular disorders [30, 31].

Although MS patients were severely disabled, they rarely reported dyspnoea [1, 4]. This might be due to severely restricted motor activity, overwhelming symptoms of fatigue or a lack of exertion-induced dyspnoea. Cognitive impairment, which is common in more advanced stages of MS, may also contribute to the low rate of reported symptoms.

Table 2. – Index of pulmonary dysfunction in multiple sclerosis

Clinical signs		Score
Patient rating		
1. History of difficulty handling mucus/secretion	No	1
	Yes	2
2. Cough	Normal	1
	Weak	2
Examiner rating		
3. Strength of patient's cough when asked to cough voluntary as forcefully as possible	Normal	1
	Weak	2
	Very weak/ inaudible	3
4. Value reached when patient counts aloud on a single exhalation after maximum inspiratory effort	>30	1
	20–29	2
	10–19	3
	<9	4
	Summed score	

Adapted from [3] with permission.

Pulmonary function

Most studies observed only slightly abnormal pulmonary function tests in patients with mild MS [1, 3, 4]. Pulmonary function (vital capacity (VC), forced expiratory volume in one second (FEV_1)) was essentially normal in ambulatory patients (Kurtze Expanded Disability Status Scale (EDSS) <7) [1–4, 32], but was reduced in wheelchair-bound and particularly in bedridden patients (fig. 1). Forced vital capacity (FVC) and maximal voluntary ventilation (MVV) were found to correlate best with the level of disability as assessed with the EDSS scores [1, 4]. The Tiffenau index (FEV_1/VC) was unaffected by disability level, indicating a restrictive pattern of pulmonary dysfunction [1, 3, 4]. Total lung capacity (TLC) and residual

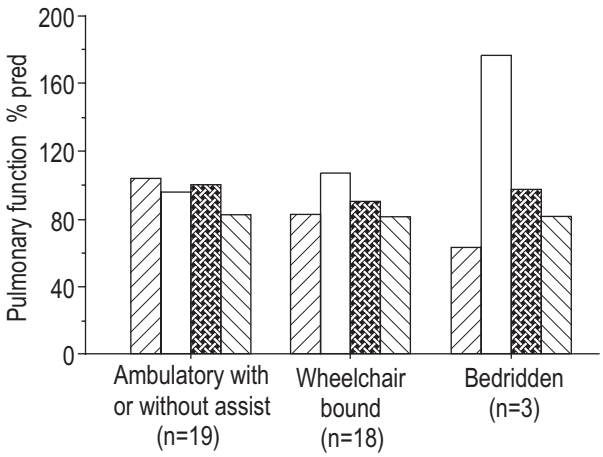

Fig. 1. – Pulmonary function tests categorized by level of disability. ▨: vital capacity; □: residual volume; ▩: total lung capacity; ▧: ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC). (Reproduced from [3] with permission.)

volume (RV) were almost normal and independent from EDSS [2–4]. It should be noted that the data on static lung volumes might be influenced by the fact that severely disabled patients were unable to perform measurements in the body plethysmograph. RV based on helium dilution measurement were significantly elevated only in bedridden patients [3]. BUYSE *et al.* [4] found no significant correlation between pulmonary function and duration of disease.

Respiratory muscle involvement

Respiratory muscle weakness was observed in a number of studies [1–4, 32, 33]. Expiratory muscles presented more severe weakness than inspiratory muscles in most studies [1, 3, 4, 32, 33], whereas others found inspiratory and expiratory muscles to be equally affected [2]. Contrary to pulmonary function tests, respiratory muscle function was also reduced in patients with mild disease. However, respiratory muscle dysfunction seemed to be the principal cause of restriction of pulmonary function. The positive correlation between both maximal expiratory and inspiratory muscle strength, (*i.e.* maximal inspiratory and expiratory pressures, $P_{I,max}$ and $P_{E,max}$, respectively) and VC supports this hypothesis [3]. Although the performance of the VC manoeuvre requires the contribution of both inspiratory and expiratory muscles, only more severe muscle weakness is associated with a proportional lung volume loss [34].

Respiratory muscle function and disability severity were studied by SMELTZER and coworkers [1, 3] in MS patients with various levels of disability. Maximal inspiratory muscle strength and MVV (a measure of respiratory endurance) were virtually normal in ambulatory patients, but significantly reduced in wheelchair-bound and bedridden patients (fig. 2). However, maximal expiratory muscle strength was reduced in all patients. These studies demonstrated that ambulatory MS patients were unlikely to have significant respiratory muscle dysfunction, whereas wheelchair-bound patients, especially those with upper extremity weakness [3], often had severely compromised respiratory muscle function. Maximal expiratory muscle strength was found to correlate best with the level of disability as assessed with the Kurtze EDSS scores. In addition, expiratory muscle weakness was significantly related to the Pulmonary Index [3] and to reduced exercise capacity [2].

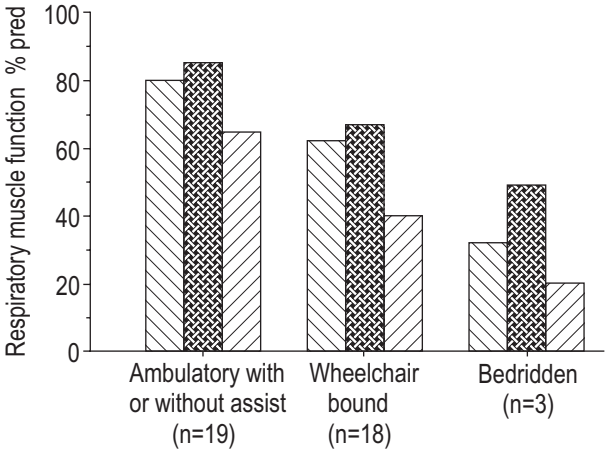

Fig. 2. – Respiratory muscle function tests categorized by level of disability. ▧: maximal voluntary ventilation; ▩: maximal inspiratory muscle strength; ▨: maximal expiratory muscle strength. (Reproduced from [3] with permission.)

Although demyelination is the most important cause of muscle weakness, other factors may also contribute to muscle weakness. Inactivity and subsequent deconditioning cause oxidative capacity to be impaired in skeletal muscles in MS [35–37]. In addition, corticosteroids have been shown to induce alterations in skeletal muscles in patients with obstructive lung disease [38]. During relapses, corticosteroids are prescribed in MS [39] and could induce skeletal muscle changes in these patients as well. Cytokines may also affect muscle function. A release of tumour necrosis factor (TNF)-α and interferon (IFN-γ) in whole-blood samples during exacerbations in MS was shown [40]. In animal experiments, TNF-α induced diaphragm dysfunction [41]. Elevated levels of TNF-α were especially present in cerebrospinal fluid (CSF) and correlated well with disability and the rate of neurological deterioration [42]. A recent study also observed a significant correlation between TNF-α messenger ribonucleic acid (mRNA) in blood mononuclear cells and disease activity [43]. In patients with polymyositis, the presence of atrophic fibres was more frequent in TNF-α-positive muscles [44]. Further research is needed to investigate the relative contribution of these factors to muscle weakness in MS.

Respiratory muscle assessment

Respiratory muscle weakness, especially expiratory muscle weakness, is common in MS and occurs in patients who are ambulatory as well as those who are confined to a wheelchair or bed. Identification of expiratory muscle weakness enables the clinician to identify patients with inadequate cough and who are at risk for upper or lower respiratory tract infections. Expiratory muscle weakness is invariably present in patients who describe difficulty in coughing or in removing airway secretions or in those with upper arm weakness observed on physical examination. These patients may perform normally on standard tests of either lung volume or maximal expiratory flow rate. Pulmonary function testing, although routinely performed, is a relatively insensitive indicator of respiratory muscle weakness. As mentioned earlier, only more severe muscle weakness is associated with a proportional lung volume loss [34]. Recent studies have suggested that the analysis of both the inspiratory and expiratory limbs of a flow–volume curve provides a specific, but not a sensitive, prediction of respiratory muscle weakness in patients with neuromuscular disease [45–47].

Another tool for the clinical assessment of respiratory muscle function is the aforementioned Pulmonary Index [3]. The best single predictor of expiratory muscle weakness was the Pulmonary Index score. Stepwise multiple regression indicated that the combination of the Pulmonary Index score, upper extremity weakness, and MVV accounted for 60% of the variance in maximal expiratory muscle strength. SMELTZER *et al.* [3] concluded that clinical assessment is a better predictor of respiratory muscle weakness than spirometry.

Systematic clinical assessment supplemented with respiratory muscle assessment and MVV can uncover subtle respiratory muscle weakness in patients with MS. BUYSE *et al.* [4] reported reliable data on maximal inspiratory and expiratory muscle strength in their patients. In patients with more severe illness, maximal mouth pressure measurement might be affected by lack of cooperation or motivation. In patients with amyotrophic lateral sclerosis the use of volitional tests was questioned as maximal inspiratory and expiratory muscle strength were found to be lower than gastric pressure during coughing or twitch stimulation [30]. The use of nonvolitional tests might be interesting, but also has its limitations (patient discomfort, position induced variability, no reference values). In addition, nonvolitional tests might overestimate expiratory muscle strength. As muscle weakness may be due to damage of the neurological pathway from the brainstem to the muscle, electrical stimulation of the nerve root or the muscle directly might overestimate the pressure development during voluntary manoeuvres which probably resemble the clinical situation more. Effective expiratory pressure generation and coughing are also dependent on the co-ordination (and spasticity) of various muscle groups.

Respiratory control

The previous paragraph suggested that some of the weakness may result from local changes in the muscle (disuse atrophy). The most important cause of muscle weakness is sclerosis and brain lesions, which may also affect breathing control. TANTUCCI *et al.* [33] performed a study on the control of breathing and respiratory muscle strength in patients with MS. In 11 stable patients with moderate-to-severe MS, ongoing for 11±7 yrs, in stable condition, and in 10 control subjects matched for age and sex, they investigated lung function and respiratory muscle strength. Ventilatory control was evaluated in terms of neuromuscular mouth occlusion pressure 0.1 s after the onset of inspiratory effort ($P0.1$) and ventilatory output ($V'E$), breathing room air and during CO_2-rebreathing. At rest, $V'E$ was similar to that of control subjects, while baseline ventilatory drive (*i.e.* $P0.1$) was significantly higher in patients. During CO_2-rebreathing, the $P0.1$/end-tidal carbon dioxide tension (P_{ET,CO_2}) slope, although less steep, was not dissimilar in patients. By way of contrast, the $V'E/P_{ET,CO_2}$ slope was much lower in the patient group and was significantly related to the functional stage of the disease and to the maximal inspiratory and expiratory muscle strength. These results suggest that in patients with clinically stable, moderate-to-severe MS, inspiratory drive at rest is increased and the drive response to CO_2 appears normal, while the ventilatory response to CO_2 is significantly impaired. However, it has to be taken into account that altered chest wall mechanics might profoundly interfere with the $P0.1$ measurement. This might alter the conclusion that respiratory muscle weakness could explain, at least in part, the lower ventilatory response in these patients.

Respiratory muscle training

As deconditioning was shown to contribute to muscle weakness, reversal by training was suggested as a treatment modality [35]. Only two reports in the literature have examined the effect of respiratory muscle training in MS patients with stable disease and respiratory muscle weakness. OLGIATI *et al.* [48] assessed, in an uncontrolled study, the effects of inspiratory and/or expiratory muscle training (RMT) on VC, maximal inspiratory, and expiratory muscle strength, and MVV. Eight patients (mean age 53 yrs) with stable disease and respiratory muscle weakness (maximal inspiratory muscle strength 64% predicted, maximal expiratory muscle strength 41% pred) underwent a 4-week RMT programme using inspiratory and/or expiratory resistive loads. Results showed significant improvements in maximal inspiratory (31%), and expiratory muscle strength (31%), and MVV (21%). As expected in patients with only moderate muscle weakness, VC remained unchanged [34]. As the study was uncontrolled, improved respiratory muscle strength and ventilatory capacity could also be attributed to learning effects. SMELTZER *et al.* [49] compared the effects of expiratory muscle training and sham training on respiratory muscle strength in 20 MS patients (EDSS ranging 6.5–9.5) with moderate to severe muscle weakness (maximal expiratory muscle strength 13–60% pred). Patients were randomly assigned to either expiratory muscle training (load intensity unknown) or sham training (the same device without an expiratory training load). Training and measurement of respiratory muscle strength were conducted at home. Ten subjects completed 3 months of expiratory training while only five subjects completed the 3 months of sham training. Respiratory muscle strength was assessed at baseline and after 1, 2, and 3 months of training. Maximal expiratory muscle strength was significantly increased (19±10%) in the expiratory training group compared to the control group. No significant change in maximal inspiratory muscle strength was observed. The results of this pilot study suggest that the strength of the expiratory muscles of MS patients may be increased through respiratory muscle training that is targeted at the expiratory muscles. Further research is indicated to determine which respiratory muscles have to be trained (inspiratory, expiratory, or both) and if increasing the strength of the respiratory muscles in MS has an effect on clinical outcomes, such as pulmonary complications and cough efficacy.

Conclusions

Pulmonary complications are commonly a source of morbidity and mortality in patients with advanced MS. Bulbar dysfunction and respiratory muscle weakness contribute to these complications. Lung function measurements usually do not allow the prediction of the occurrence and, in particular, the degree of respiratory muscle weakness. Despite this notion, measurement of the maximal inspiratory and expiratory pressures has not yet become an integrated part of the clinical examination of patients with MS. The value of nonvolitional tests has yet not been substantiated.

The use of an index of pulmonary dysfunction may be useful in identifying asymptomatic patients with MS with pulmonary dysfunction and therefore, at risk for pulmonary complications. There is a correlation between pulmonary dysfunction and the stage of neurological disability, but no correlation is seen between pulmonary dysfunction and the duration of disease. Several studies have demonstrated

that ambulatory MS patients were unlikely to have significant pulmonary dysfunction, whereas wheelchair-bound patients, especially those with upper extremity weakness, often have severely compromised respiratory function.

Since inspiratory and expiratory muscle weakness is present and in part related to inactivity, training of respiratory muscles could be effective to improve respiratory muscle function. Whether respiratory muscle training enhances ventilatory pump capacity, delays the development of respiratory dysfunction, and subsequently can improve exercise capacity and cough efficacy, prevents pulmonary complications or prolongs survival in the long-term remains to be determined. The instability of the clinical picture often seen in patients with multiple sclerosis, may render proper evaluation of the effect of respiratory muscle training difficult.

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