Pulmonary Dysfunction, Assessment, and Treatment in Multiple Sclerosis

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***Pulmonary muscle weakness is a symptom of multiple sclerosis (MS) that begins early in the disease process, although it is often not recognized by health-care providers until later stages. Standard pulmonary function tests are not effective in detecting this reduction in pulmonary muscle strength. Maximal inspiratory and expiratory pressures are indirect measures of pulmonary muscle strength that are effective in detecting early changes. Once detected, pulmonary muscle weakness is effectively treated with pressure threshold load inspiratory and expiratory muscle exercises that can be implemented using inexpensive handheld pressure threshold load muscle training devices. These exercises require little time and are effective in patients with any level of disability. Int J MS Care.* 2010;12:97–104.**

Multiple sclerosis (MS) is a disease of the central nervous system. Signs and symptoms and the accumulation of disability are due to demyelination and axonal injury.[1] Multiple sclerosis affects not only muscles of the limbs and trunk but also muscles of respiration. Muscle weakness, changes in muscle tone, motor incoordination, and postural abnormalities all reduce pulmonary function. In the majority of patients with mild-to-moderate disability associated with MS, central motor conduction to the diaphragm muscle is abnormal.[2] Respiratory impairment in neurologic or neuromuscular injuries or disorders such as MS includes 1) difficulty in ventilation due to inspiratory muscle weakness; 2) difficulty in coughing due to weakness of the expiratory muscles, upper-airway (glottic) muscle, and inspiratory muscles; and 3) risk of aspiration of fluids due to upper-airway muscle weakness.[3]

Actual prevalence rates of respiratory problems in individuals with MS are not known[4]; however, due to the prevalence of MS in the United States (approximately 400,000) and worldwide (2.5 million), a significant number of individuals may be at risk.[5] Very few studies address differences in respiratory impairment relative to type of MS, although Grasso et al.[6] reported greater respiratory abnormalities in patients with cerebellar involvement.

Patients with MS rarely complain of pulmonary dysfunction, although upon testing pulmonary dysfunction is commonly found.[7] Pulmonary muscle strength is often reduced even in patients with mild disease.[8-12] Pulmonary compromise affects as many as 52% of recently diagnosed individuals with MS.[13,14] Pulmonary muscle involvement occurring early in the course of the disease is due largely to reversible neuromuscular failure.[10] Indirect measures of pulmonary muscle strength (maximal inspiratory pressure [MIP] and maximal expiratory pressure [MEP]) are significantly reduced in patients with MS. In ambulatory patients with MS, average MIP values range from 55% to 77% of predicted values, and average MEP values range from 34% to 60% of predicted values. In patients with MS who are either confined to bed or primarily use a wheelchair, average MIP values range from 27% to 74% of predicted values, and average MEP values range from 18% to 51% of predicted values.[12] Pulmonary muscle endurance is measured indirectly by maximal voluntary ventilation (MVV). Average MVV values range from 91% to 95% of predicted values in ambulatory patients with MS and are approximately 68% of predicted values in those who are confined to bed or primarily use a wheelchair.[12,15]

Respiratory compromise including acute respiratory failure, previously considered a condition rarely associated with MS, has been found to be common in MS, particularly during the terminal stage.[9,10,16,17] Acute respiratory failure may occur in patients with moderate-

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to-severe respiratory muscle weakness and in those challenged by relatively minor added respiratory loads, such as that associated with an otherwise uneventful respiratory infection.[9,16,17] Due to progressive decrease of motor efficiency, restrictive symptoms reduce the vital capacity (VC), inspiratory and expiratory flows, and MVV.[14]

Assessment of Respiratory Function

Full pulmonary function tests are often conducted by pulmonologists. However, in traditional pulmonary function testing protocols, respiratory muscle strength, measured by MIP and MEP, is often not included. Physical therapy offices that have appropriate testing equipment can easily include both spirometry and tests of respiratory muscle strength in their regular examination of a patient with MS (Table 1). This typically does not increase patient cost because it is charged under the physical therapy examination *Current Procedural Terminology (CPT)* code 97001.

Spirometry

As noted previously, respiratory complaints may not be forthcoming from individuals with MS even though, upon testing, impairment of pulmonary muscle function is evident.[7,18] Assessment of pulmonary function is typically conducted using a spirometer, with the patient performing prolonged (3–6 seconds) and forceful expiratory maneuvers (Table 1). Spirometry tests dynamic pulmonary function parameters such as forced vital capacity (FVC), forced expiratory volume in the first second of expiration (FEV_1), FEV_1/FVC ratio, MVV, and peak expiratory and peak inspiratory flow (PEF and PIF, respectively).[19] However, standard spirometry measurement of pulmonary function values in people with MS are typically normal until there is a 50% or greater loss of respiratory muscle strength.[15,20] Thus, standard spirometry is not a sensitive measure of respiratory muscle strength in the MS population. In an attempt to modify standard spirometry protocols to increase sensitivity in people with neuromuscular disorders, Altintas et al.[7] studied minimally disabled patients with MS (mean Expanded Disability Status Scale [EDSS] score, 2.9) who had no respiratory complaints. They reported that the difference between FVC in the upright versus supine positions was 7.13% in the subjects with MS, compared with 2.49% in the normal controls. The greater difference for the patients with MS is consistent with previous research conducted in patients with amyotrophic lateral sclerosis.[21] Thus, determining the difference between upright and supine FVC values may be useful in assessing early respiratory impairment in people with MS.

Grasso et al.[6] reported that respiratory impairment was common in people with MS, with a prevalence ranging from nearly 36% in ambulatory patients to nearly 83% in nonambulatory patients. They found that MVV was more sensitive than FVC or FEV_1 as an indicator of respiratory impairment. Thus, MVV and tests of pulmonary muscle strength (MIP and MEP) are strong indicators of early pulmonary muscle impairment in MS.

Table 1. Assessment of pulmonary function and respiratory muscles

Function tested	Assessment method	Equipment required
FVC	Maximal volume of air forcibly blown out after full inspiration	Spirometer[a]
FEV_1	Maximal volume of air forcibly blown out in the first second during the FVC test	Spirometer
FEV_1/FVC ratio	Percentage of FVC expired in the first second of maximal expiration	Spirometer
PEF and PIF	Maximal forced expiration rate from full inspiration and maximal inspiration rate from full expiration	Spirometer
MVV	Maximal amount of air inhaled and exhaled in 1 min	Spirometer
MIP and MEP	Pressure generated during maximal inspiration or expiration	Manometer[b]

Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MVV, maximal voluntary ventilation; PEF, peak expiratory flow; PIF, peak inspiratory flow.

[a]Spirometers range in cost from $400 to $5200 depending on extent of function.

[b]The MicroRPM (Respiratory Pressure Meter) manometer (CareFusion [formerly Micro Medical], Basingstoke, UK) costs $1200.

Respiratory Muscle Assessment

Reduced pulmonary muscle function is observed in individuals with MS in the presence of little or no impairment demonstrated on standard pulmonary function tests.[22] Evaluation of respiratory muscle function early in the course of MS may enable prevention of respiratory complications.[7,19,23] Patients with MS who have a combination of reduced maximal respiratory pressures and FVC should be monitored via serial respiratory muscle pressure and FVC tests.[7] A joint statement on the art of respiratory muscle assessment has been

issued by the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[24] The ATS/ERS guidelines for respiratory muscle testing recommend using a digital manometer, rather than an aneroid (mechanical) manometer.[24] Currently there is only one commercially available handheld digital manometer specifically for respiratory pressure measurement—the MicroRPM (Respiratory Pressure Meter; CareFusion [formerly Micro Medical], Basingstoke, UK) (Figure 1). The MicroRPM measures MEP and MIP at the mouth and sniff nasal inspiratory pressure (SNIP) by having the patient produce a maximal voluntary expiratory and inspiratory effort. The number of trials needed to achieve adequate MEP and MIP measurements is variable. The ATS/ERS statement recommends three trials.[24] Fiz et al.[25] stated that as many as nine trials in a single practice session may be required in patients with respiratory disease. Smeltzer and Lavietes[26] recommended two practice sessions, each consisting of ten trials per session, before identifying a baseline. Order of performance does not affect the MIP and MEP values.[27] The ATS/ERS statement recommends that the inspiratory and expiratory pressure be maintained for at least 1.5 seconds, so that the maximum pressure sustained for 1 second can be recorded.[24] MIP and MEP measures typically can be completed within 10 to 20 minutes in the clinic using the handheld MicroRPM testing device, depending on the individual patient's muscle strength, fatigability, and coordination.

Figure 1. **The MicroRPM (Respiratory Pressure Meter) respiratory muscle strength assessment device (CareFusion [formerly Micro Medical], Basingstoke, UK)**

Neurophysiologic Techniques

Neurophysiologic techniques such as magnetic transcranial stimulation, magnetic cervical stimulation, and electrical stimulation of the phrenic nerve at the neck to assess motor evoked potentials (MEPs) and central motor conduction time (CMCT) between the cortex and the diaphragm have been used in a limited number of studies in individuals with MS. Investigators reported prolonged MEPs and CMCTs.[28,29] Additionally, it was noted that the electrophysiologic study of the diaphragm was abnormal in some patients with MS who exhibited no pulmonary symptoms and had normal pulmonary function.[28]

Assessment Frequency

Assessment of pulmonary muscle function is recommended at initial diagnosis of MS to establish a baseline and then at the time of any pulmonary infection, onset of dyspnea on exertion, or reduction in physical performance.[6,30] Grasso et al.[6] suggested that patients with cerebellar impairment receive serial evaluation of respiratory function to determine whether impairment is present.

Respiratory Muscle Training

Principles of muscle strength training that apply to limb and trunk muscles also apply to muscles of respiration. A fundamental principle of exercise physiology is that to gain strength, one must use progressive resistance to overload the muscle during exercise.[31] Breathing exercises without resistance are not sufficient to significantly increase respiratory muscle strength. For example, Wiens et al.[32] reported nonsignificant increases in respiratory function following thrice-weekly music therapy emphasizing diaphragmatic breathing and coordination of breath and speech for patients with advanced MS (EDSS scores 7.0–9.5). Typically, pulmonary muscle training is performed using either inspiratory or expiratory muscle pressure threshold load trainers (Tables 2 and 3). Studies comparing the value of inspiratory versus expiratory training in patients with MS have not yet been conducted. The rationale for selecting an inspiratory muscle trainer (IMT) is that weakened inspiration predisposes the respiratory muscles to fatigue and contributes to perceived dyspnea. Inspiratory muscle training also increases MIP and reduces dyspnea (rest and exercise).[38] The rationale for selecting an expiratory muscle trainer (EMT) is to build expiratory force to support productive coughing and voice production. Measurement of respiratory muscle strength should show carryover between

Table 2. Respiratory muscle training protocols in individuals with multiple sclerosis

Study	Method used and type of training	No. of subjects	EDSS score	Frequency	Duration	Initial intensity	Sets and repetitions	Basis of training progression advancement
Olgiati et al.,[33] 1989	Resistive (I and/or E)	5 amb 3 w/c	Not specified	Twice daily	4 ± 1 wks	Given mean target pressure, not specified	2 periods of 3–5 min	Not specified
Smeltzer et al.,[34] 1996	PTL (E)	10 T 5 C	6.5–9.5	Twice daily	12 wks	Based on MEP, did not specify value	3 sets of 15 reps	Tolerance to exercise
Wiens et al.,[32] 1999	Music therapy	9 T 10 C	7.0–9.0	Once per day, 3 d/wk	12 wks	Not applicable	Three 30-min sessions/wk	Not applicable
Gosselink et al.,[35] 2000	PTL (E)	9 T 9 C	7.0–9.5	Twice daily	12 wks	60% MEP	3 sets of 15 reps	60% of MEP adapted twice daily, combined with daily physical therapy
Chiara et al.,[11,36] 2006, 2007	PTL (E)	17 MS 14 HC	1.5–6.5	Once per day, 5 d/wk	8 wks	40% MEP	4 sets of 6 reps	MEP of individual: 40% 1st wk, 60% 2nd wk, 80% 3rd–8th wks
Klefbeck & Hamrah Nedjad,[37] 2003	PTL (I)	7 T 8 C	6.5–9.0	Twice every other day	10 wks	40–60% MIP	3 sets of 10 reps	MIP and RPE
Fry et al.,[12] 2007	PTL (I)	20 T 21 C	2.5–6.5	Daily	10 wks	30% MIP	3 sets of 15 reps	MIP and RPE

Source: Adapted with permission from Fry et al.[12]
Abbreviations: amb, ambulatory; C, control subjects; E, expiratory; EDSS, Expanded Disability Status Scale; HC, healthy controls; I, inspiratory; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MS, multiple sclerosis; PTL, pressure threshold load; RPE, rating of perceived exertion; T, trained subjects; w/c, wheelchair-bound subjects.

inspiration and expiration, thus benefiting both functions. Some clinicians choose an IMT or EMT based on MIP and MEP values of the individual patient, selecting the device that will strengthen the patient's weakest muscles.[33] Although large-scale studies have not yet been conducted on the use of pressure threshold load breathing exercises in people with MS, several smaller studies yielded consistent results supporting the use of either inspiratory or expiratory pressure threshold load exercise to improve pulmonary muscle strength across a wide range of disability levels.[11,12,34-37,39]

Use of either an IMT or an EMT is supported for ambulatory individuals with MS (EDSS scores <6.5). In a study of 46 ambulatory people with MS (EDSS scores 2.5–6.5), Fry et al.[12] trained participants daily for 10 weeks with an IMT device. Significant improvements in MIP (80.9% increase) and nonsignificant increases in MEP (21.4%) and MVV (9.0%) were noted in the IMT-trained participants. Likewise, Chiara et al.,[11,36,39] who trained 17 ambul tory individuals with MS (EDSS scores 1.5–6.5) 5 days a week for 8 weeks using an EMT device, found significant increases in MEP (37.4% in the mild disability group and 44.1% in the moderate disability group) and nonsignificant increases in MIP.

Use of either an IMT or an EMT is also supported for people with more advanced MS (EDSS scores >6.0). In a study of 15 patients with advanced MS disability (EDSS scores 6.5–9.0), Klefbeck and Hamrah Nedjad[37] administered inspiratory training to 7 of the participants every other day for 10 weeks. Both MIP and MEP values increased significantly from baseline in the trained participants, and MIP values were significantly more improved in the trained than in the control group participants. Two independent studies found

Table 3. Commercially available pressure threshold load (PTL) respiratory muscle trainers

Trainer	Manufacturer	Models/ versions	Resistance	PTL range (cm H_2O)	Cost
Inspiratory Muscle Trainers					
Inspiratory Muscle Trainer (IMT)	Philips Respironics	1	Light	9–41	$225 10 units/case
POWERbreathe	HaB International Ltd.	Plus/3			$80/unit
Wellness			Light	17–98	
Fitness			Medium	23–186	
Sports Performance			Heavy	29–274	
Inspiratory/Expiratory Muscle Trainers					
Positive Expiratory Pressure (PEP)	Philips Respironics	1	Very light	5–21	$225 10 units/case
PowerLung	PowerLung				
Active Series					
AireStream			Very light	2–19	$89/unit
BreatheAir			Light	4–93	$99/unit
Trainer			Medium	4–95	$109/unit
Sport			Very heavy	78–678	$119/unit
Performer Series					
T343A Teal			Light		$99/unit
P617B Purple			Medium		$109/unit
M422T Orange			Very heavy		$119/unit
Expiratory Muscle Trainers					
Aspire EMST 150	Aspire Products	1	Medium	15–150	$45/unit
Respi-aide EMT-1	GaleMed Corp		Very light	5–20	$22–27/unit
Respi-aide EMT-2			Very light		

Abbreviation: cm H_2O, centimeter of water (the unit of pressure measurement used in the PTL trainers).
Note: A list of manufacturers and products included in this table, along with manufacturer websites, appears at the end of the article.

that expiratory training produces pulmonary muscle strength gains in people with advanced MS disability. Smeltzer et al.[34] provided expiratory training to 10 of 15 individuals with advanced MS (EDSS scores 6.5–9.5). Participants completed two sessions of training daily for 3 months. The trained participants significantly increased their MEP values, but significant changes in MIP were not observed.[34] Likewise, Gosselink et al.[35] provided expiratory training to 9 of 18 individuals with advanced MS disability (EDSS scores 7.0–9.5) twice daily for 3 months. The patients' MIP values increased significantly compared with baseline but were not significantly improved compared with the control group. The MEP values increased, but not significantly, in the EMT group.

In summary, studies find relatively consistent significant increases in strength of trained respiratory muscles (inspiratory or expiratory), with some nonsignificant carryover increases in strength of the nontrained muscles. Other benefits of inspiratory and expiratory training for people with MS identified as secondary outcomes in research studies and/or participant observations include increased frequency of conscious performance of deep breathing,[34] deeper respirations,[34] less shortness of breath in the supine position,[34] stronger voice,[34] and improved quality of life secondary to having a stronger voice.[36,39] Moreover, benefits extend beyond the respiratory system. Fry-Welch et al.[40] noted improved static standing balance and mobility function following inspiratory training in ambulatory individuals with MS.

Respiratory Muscle Trainers

Extensive literature on respiratory muscle training details the advantages and disadvantages of the different types of trainers, including incentive spirometer,[41,42] isocapnic hyperpnea,[43,44] resistive,[45,46] and pressure threshold load devices.[47,48] The pressure threshold load trainers are the most highly recommended type of trainer[47,49-51] and have been available since the late 1980s (Figure 2).[52] An advantage of the pressure threshold

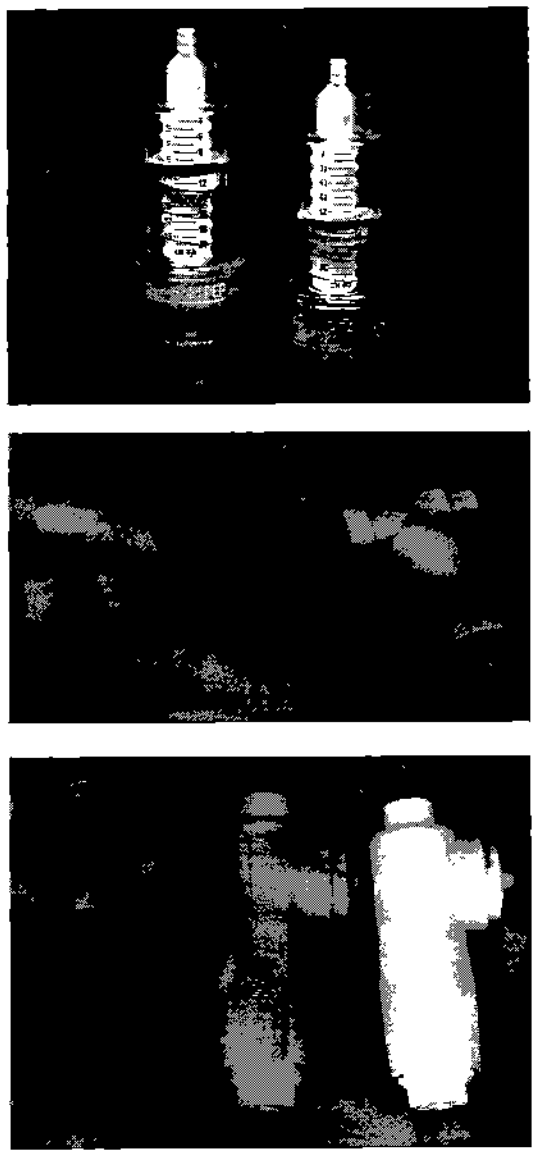

***Figure 2.* Examples of pressure threshold load respiratory muscle trainers**

A, Threshold Positive Expiratory Pressure (PEP) and Threshold Inspiratory Muscle Trainer (IMT) (Philips Respironics, Murrysville, PA). B, POWERbreathe (HaB International Ltd, Southam, Warwickshire, UK). C, PowerLung (PowerLung, Houston, TX).

trainers is that the resistance remains constant independent of air flowing through the device so that a patient cannot simply breathe more slowly to reduce the amount of resistance. Pressure threshold load levels can also be readily adjusted by the patient to increase the amount of resistance. The devices range in level of resistance provided, with lower resistance offered by the Threshold Inspiratory Muscle Trainer (Phillips Respironics, Murrysville, PA) and higher resistance offered by the POWERbreathe (HaB International Ltd, Southam, Warwickshire, UK) and the PowerLung (PowerLung, Houston, TX) (Table 3). Costs for the training devices range from $25 to $100 for units commonly used clinically, making this an inexpensive device for home use.

Limitations of Existing Research and Future Research Needs

Limitations in the studies that have examined respiratory muscle training in individuals with MS include limited subject populations (range, 8–46), variable training protocols (ie, intensity, duration, and frequency), and limited documentation of retention of exercise effects if exercise is discontinued. In addition, existing reports mainly focus on impairment outcomes, with very limited research on functional outcomes.

Many additional clinical research questions need to be answered to guide evidence-based clinical treatment of pulmonary muscle impairment in people with MS. Relationships between pulmonary function and physical performance levels must be better delineated. Additional studies addressing optimal training duration, frequency, and intensity and retention of training effects are necessary. Comparisons of inspiratory versus expiratory training and combined inspiratory/expiratory training, as well as comparisons of strength versus endurance and combined strength and endurance protocols, will help more clearly define the most effective pulmonary muscle exercise protocols. Studies outlining any differential effects of training based on type of MS (relapsing remitting, secondary progressive, primary progressive, and progressive relapsing) and disability status (EDSS scores) will help guide clinical decision making in the future.

PracticePoints

- Pulmonary muscle strength is impaired even in early stages of MS-related disability.
- Standard pulmonary function tests are not sensitive to early changes in pulmonary muscle function. Testing of maximum inspiratory and expiratory pressures should be included in any assessment of pulmonary function in people with MS.
- Resisted inspiratory and expiratory muscle training are effective in increasing pulmonary muscle strength in both early and advanced stages of MS.

Conclusion

Recent research established the presence of pulmonary muscle weakness early in the MS disease process. The results of standard pulmonary function tests typically remain within normal ranges until there is a 50% or greater loss of pulmonary muscle strength. Thus, it is imperative that other forms of pulmonary testing be used early in the disease process. Maximal inspiratory and expiratory mouth pressures are effective measures of this early pulmonary muscle strength impairment in individuals with MS. Patients with any level of MS-related disability can improve their pulmonary muscle strength through resisted inspiratory and/or expiratory muscle training. The training devices are inexpensive and easily used by patients with MS. □

Manufacturers of Products Mentioned

Aspire Products (Aspire EMST 150), Gainesville, FL. http://www.aspireproducts.org

CareFusion (formerly Micro Medical) (MicroRPM [Respiratory Pressure Meter]), Basingsloke, UK. http://www.micromedical.co.uk

GaleMed Corporation (Respi-aide EMT; not currently available in the United States), Taipei, Taiwan. http://www.galemed.com

HaB International Ltd (POWERbreathe), Southam, Warwickshire, UK. http://www.powerbreathe.com

Phillips Respironics (Threshold Inspiratory Muscle Trainer [IMT], Threshold Positive Expiratory Pressure [PEP]), Murrysville, PA. http://threshold.respironics.com

PowerLung (PowerLung), Houston, TX. http://www.powerlung.com/region/us

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