Training of Respiratory Muscles in Patients With Multiple Sclerosis: A Systematic Review

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BACKGROUND: The aim of this systematic review was to summarize the level of evidence and grades of recommendation regarding therapeutic respiratory muscle training interventions in patients with multiple sclerosis (MS). METHODS: We conducted a search using a number of electronic databases, and the limits of the search were studies published between 1993 and 2013. The selected documents were classified according to grades of recommendation of the Finnish Medical Society Duodecim. The methodological quality of 11 studies was assessed using the Physiotherapy Evidence Database (PEDro) scale. RESULTS: Fifteen trials (6 randomized controlled trials [RCTs], 2 non-RCTs, one quasi-experimental trial, 3 case studies, and 3 systematic reviews) showed clinical changes from pulmonary function outcomes for MS. The reviewed articles covered training protocols that were carried out for 10 weeks to 3 months at a frequency of 7 d/week with one or 2 daily sessions consisting of 3 sets of 10 or 15 repetitions per set at an intensity of 10–60% of the subject's maximum expiratory pressure. It was observed that subjects who had minor scores in the Kurtzke Expanded Disability Status Scale showed changes in maximum inspiratory and expiratory pressures after respiratory muscle training. In future studies, it would be suitable to take into account both inspiratory and expiratory muscle training. *Key words: multiple sclerosis; inspiratory muscle training; neuromuscular disorder; respiratory muscle training; expiratory muscle strength training; breathing exercise; threshold trainer.* [Respir Care 2014;59(11):1764–1772. © 2014 Daedalus Enterprises]

Introduction

Multiple sclerosis (MS) is a primary, chronic, inflammatory, and progressive disease caused by the demyelination of the central nervous system that may affect motor pathways and cause muscle weakness, respiratory muscles included.[1-8] The demyelinated plaques have a predilection for the optic nerves, brainstem, spinal cord, and periventricular white matter. This disease affects mostly young and middle-aged adults. MS is confirmed through laboratory tests.[6]

Not only is MS one of the most common central nervous system diseases and the most frequent neurological disease among young adults, it is also the second cause of disability in people 20–40 y old.[9] The prevalence worldwide is ~30 people per 100,000 inhabitants, which is equivalent to 2,500,000 patients worldwide, 600,000 in Europe and 46,000 in Spain.[9] It occurs more in women than in men at an approximate 2:1 ratio.[10]

Respiratory complications have been recognized as the major cause of morbidity and mortality in individuals with advanced MS.[2,5] Of those people with MS who died before age 50, pneumonia and influenza were the cause of death in 20% of the cases. Gosselink et al[8] showed the direct connection between respiratory muscle function and the

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level of a patient's disability. In addition to this, bedridden patients presented worse levels of maximum voluntary ventilation and inspiratory and expiratory muscle strength compared with wheelchair-bound patients and ambulatory patients without assistance.

Research testing the use of respiratory muscle endurance and/or strength training in athletes, healthy individuals, and patient populations has been documented.[11] Moreover, there are many different types of devices for respiratory muscle training that improve inspiratory and expiratory muscle strength.[11] Despite the variety of studies, the optimal training scheme has yet to be defined. The specification of the loads to be imposed during training is the main factor that determines the outcome. Thus, high intensity and infrequent stimuli will bring about an increase in the strength derived from improving fiber and muscle size. In contrast, moderate repetitive efforts result in increased muscle strength by enlarging the elements involved in aerobic muscle activity. Previous clinical trials supported the effectiveness of low-to-moderate intensity inspiratory muscle training (maximum of 38 cm H_2O) alone and in combination with aerobic exercise.[12] One study supports the idea that, for the initial 2-min interval, a training load should be selected equivalent to 30% of a patient's maximum inspiratory pressure (P_{Imax}). Loads < 30% of P_{Imax} are insufficient to induce improvement in inspiratory muscle strength. Loads that patients described as somewhat difficult are selected. On completion of the first training session, patients are often trained at loads equal to ~40% of P_{Imax}. The inspiratory load can usually be increased rapidly during the first 4 weeks of training, largely as a consequence of neurosensory adaptation reflecting desensitization to the inspiratory loads and improved recruitment of motor units.[13]

The main aim of this study was to summarize the level of evidence and grades of recommendation regarding therapeutic respiratory muscle training interventions in patients with MS. Hence, it is necessary to develop the most suitable protocol to improve respiratory muscle weakness and respiratory function based on the use of values in order to propose a treatment plan in which the duration, frequency, and most suitable intensity are specified, as well as the aspects that are important according to the aims of the therapist.

Methods

Literature Search

A literature search was carried out to identify all possible studies that could help to answer the research question. The following databases were searched for relevant studies: MEDLINE (Ovid), PEDro, OAIster, Scopus, PsycINFO, Web of Science, CINAHL (EBSCOhost), SPORTDiscus (EBSCOhost), Directory of Open Access Journals (DOAJ), Cochrane, Embase, Academic Search Complete (EBSCOhost), Fuente Académica (EBSCOhost), and MedicLatina (EBSCOhost). In addition, the reviewer conducted a manual search of the revised reference lists of identified articles and published conference abstracts.

Two reviewers carried out several searches in the databases using combinations of key words: multiple sclerosis, neuromuscular disease, respiratory muscle training, breathing exercises, inspiratory muscle training threshold trainer, expiratory muscle strength training. The searches were limited to English studies reported between 1993 and 2013. Randomized controlled trials (RCTs), non-RCTs, quasi-experimental trials, case studies, and systematic reviews were included, and articles that did not use threshold trainers were excluded.

Inclusion and Exclusion Criteria

Inclusion criteria were constructed using the PICO (population, intervention, control/comparison, and outcomes) model. First, the population included samples of people independent in activities of daily living and wheelchair or bedridden patients with MS.[2,8] Second, the intervention included inspiratory and expiratory exercises of different intensities and duration through a resistance offered by a value threshold, adapting to the needs and changes of the individual while progressing through the study. Third, different types of RCTs, non-RCTs, cohort, and quasi-experimental trials, systematic reviews, and case studies were included. Different types of interventions (maximum and controlled inspirations, maximum and controlled expirations, and non-intervention) were also included.[1-7,14-17] Finally, the outcomes also included were functional outcomes (P_{Imax}, maximum expiratory pressure [P_{Emax}], respiratory muscle strength), physical capacity (6-min walk test [6MWT]),[3,4] clinical outcomes (severity of the disease, Kurtzke Expanded Disability Status Scale [EDSS]), and other outcomes such as the duration of sustained vowel prolongation and number of words/min.[1] Studies were excluded if they dealt with other diseases such as asthma, chronic airway obstruction, pulmonary emphysema, cystic fibrosis, coronary insufficiency, and chronic pain[1,6,7]; pulmonary or musculoskeletal instability and previous history as a smoker[1,4,5]; and COPD, tuberculosis, and chronic bronchitis.[3]

Assessment of Methodological Quality

Seventeen relevant articles were found in the main databases. Fifteen original studies were examined after subsequent selection based on the title and abstract. After analyzing the primary documents, 12 were relevant to this review, as were 3 systematic reviews. Two articles were excluded after reading the summaries because they did not make specific reference to patients with MS.

Table 1. PEDro Score for Methodological Quality Assessment of 12 Studies

Section/Topic	Study											
	Chiara[1]	Gosselink[2]	Mutluay[3]	Pfalzer and Fry[4]	Fry[5]	Klefbeck and Hamrah Nedjad[6]	Smeltzer[7]	Smeltzer and Lavietes[14]	Bosnak-Guclu[15]	Foglio[16]	Buyse[17]	Ray[27]
Eligibility criteria	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Randomly allocated	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Concealed allocation	No	No	Yes	Yes	No	No	No	No	No	No	No	No
Comparability of base	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Blinding of subjects	No	No	No	No	No	No	No	No	No	No	No	No
Blinding of therapist	No	No	No	No	No	No	No	No	No	No	No	No
Blinding of assessor	No	No	Yes	No	Yes	No	No	No	Yes	No	Yes	No
Proper continuation	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Intention to treat	No	No	No	No	No	No	Yes	Yes	Yes	No	No	Yes
Between-group statistical comparison	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Point measure and measures of variability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Total	3	5	7	6	6	5	4	4	6	3	2	5

Note that the item of eligibility criteria does not contribute to the total score.

The methodological quality of the 12 studies was evaluated using the PEDro scale.[18-20] Two independent reviewers (Zamora-Pascual and Martín-Valero) completed the assessment list based on the PEDro score. This scale (0–10) is based on the list developed by Verhagen et al[21] and assesses the internal validity of RCTs. A study with a PEDro score of 6 or more is considered level-1 evidence (6–8: good; 9–10: excellent), and a study with a score of 5 or less is considered level-2 evidence (4–5: fair; < 4: poor).[22]

The articles included in this review had PEDro scores of 3–7, as shown in Table 1. Trials were considered to be of high enough methodological quality if they had a score of at least 5 points. This was based on the fact that the tests with a score close to 4 do not employ a triple-blind methodology (ie, patient, evaluator, and provision of treatment). With this evaluation, we found 6 RCTs with scores of 4–7, 2 non-RCTs with a score of 3, one quasi-experimental study, 3 case studies, and 3 systematic reviews.

Evaluation of Clinical Relevance

Analysis of the effect size values was performed to compare the different types of interventions for MS. The effect size was calculated using the following formula of 11 original studies: (mean posttest outcomes of type A intervention) − (mean posttest outcomes of type B intervention).[23] Analysis of the effect size values was based on Cohen's work,[23] which determined that values below 0.2 were considered to have no effect, those between 0.2 and 0.5 a small effect, those between 0.5 and 0.8 a medium effect, and those above 0.8 a major effect.

The grades of recommendation were studied according to the Finnish Medical Society Duodecim (Duodecim), a clinical practice guide developed in Finland to improve the quality of healthcare.[24] Grade A means that the recommendation is based on strong evidence; grade B means that the recommendation is based on sufficient evidence to make a clear recommendation; grade C recommendations are based on limited evidence; and grade D refers to recommendations for which there is no evidence based on clinical studies.[25] In all cases, P values < .05 were taken as significant.

Results

The 15 reviewed articles covered treatment protocols with a threshold trainer that were carried out for 10 weeks to 3 months at a frequency of training of 7 d/week with one or 2 daily sessions consisting of 3 sets of 10 or 15 repetitions per set at an intensity of 10–60% of P_{Emax}. The results of this review are presented in Table 2. A meta-analysis of the data of the RCTs was included in this review and is provided in Figure 1.

Discussion

Respiratory muscle training may improve respiratory muscle function in patients with MS. However, the paucity of studies in the area and the variability between them are limiting factors. The aim of this systematic review was to

Table 2. RCTs on the Effectiveness of a Threshold Trainer in Respiratory Muscle Weakness Training of Patients With MS

Reference	PEDro Scale (n)	Type of Evidence	DR	Main Intervention	Intra-group Variables	Effect Size, Functional Variable	Effect Size, Clinical Variable
Mutluay[3]	7–10 (40)	RCT	A	BEUEE 6 wk 30 min/d	↑ P_{Imax} ($P > .01$) ↑ P_{Emax} ($P = .007$) PDI ($P = .002$) 6MWT ($P = .03$) FVC ($P = .036$)	P_{Imax} 7.1% P_{Emax} + 4.8% PDI − 9% 6MWT + 13% FVC 4.8%	↓ BS 14.5 ↓ EDSS 4
Pfalzer and Fry[4]	6–10 (46)	RCT	A	10 wk 7 d/wk 3 sets of 15 inspirations/d	↑ P_{Imax} ($P = .003$) P_{Emax} ($P = .34$) MVV ($P = .12$) 6MWT ($P = .09$)	P_{Imax} 71.4% P_{Emax} 21.0% MVV 9.0% BAL ($P = .01$)	↑ EDSS 4.3 ↓ FSS 47.7
Fry[5]	6–10 (41)	RCT	A	10 wk 7 d/wk 3 sets of 15 inspirations/d	↑ P_{Imax} ($P < .001$) P_{Emax} ($P = .29$) MVV ($P = .14$) ↑ $FEF_{25-75\%}$ ($P = .003$)	P_{Imax} 80.9% P_{Emax} 21.4% MVV 9% (1/min)	EDSS 4 FSS 5.2
Klefbeck and Hamrah Nedjad[6]	5–10 (15)	RCT	A	10 wk 2 sessions/d 3 sets of 10 inspirations/session 1-m rest between sets	↑ P_{Imax} ($P < .008$) ↑ P_{Emax} ($P < .02$)	P_{Imax} 25 cm H_2O* P_{Emax} 17 cm H_2O*	↓ BS 12 EDSS 8.5 ↓ FSS 5.2
Gosselink[2]	5–10 (P1: 9; P2: 9)	P1 survey/P2 RCT	A	P2: 3 mo 7 d/wk 2 sessions/d 3 sets of 15 expirations/session Intensity of 60% of P_{Emax}	P1: ↑ FVC ($P < .001$) ↑ P_{Imax} ($P < .01$) ↑ P_{Emax} ($P < .001$) ↑ PI ($P < .05$) P2: ↑ P_{Imax} ($P < .05$) P_{Emax} ($P = .08$) PDI ($P = .41$)	P1: FVC 43% P_{Imax} 27% P_{Emax} 18% P2: P_{Imax} − 9% P_{Emax} 8% PI 0.2%	EDSS 8.5
Smeltzer[7]	4–10 (15)	RCT	A	3 mo 7 d/wk 2 sessions/d 3 sets of 15 expirations/session Intensity of 10% of P_{Emax} 5 min rest between sets	↑ P_{Emax} ($P = .003$)	P_{Emax} 19.4 cm H_2O	EDSS 6.5–9.5
Gosselink[8]	0–10	Systematic review	A	0	PDI (r=0.70, $P < .001$)	AMB, WB, BR (approximate): VC 105, 80, 65% RV 97, 110, 175% TLC 100, 90, 100% FEV_1/FVC 83, 83, 83% MVV 80, 63, 35% MIMS 85, 67, 50% MEMS 65, 40, 20%	EDSS < 7
Sapienza[11]	0–10	Systematic review	A	4–8 wk 20–30 min/d	0	4 wk: P_{Emax} ↑ 41% 8 wk: P_{Emax} ↑ 50%	0
Sapienza and Wheeler[26]	0–10	Systematic review	A	5 d/wk 5 sessions/d 15–20 min/d Intensity of 75% of P_{Emax}	0	0	0
Chiara[1]	3–10 (31)	Non-RCT	B	3 SEs (2 with PwMS, 1 with HC) P_{Emax} (standing) 8 wk 5 d/wk 4 sets of 6 repetitions/d Intensity of 80% of P_{Emax}	P_{Emax} ($P > .05$) SVP ($P > .05$) Words/min ($P > .05$)	PwMS P_{Emax} 40.4% HC P_{Emax} 29.2%	DVRQLM ($P = .005$) ALSSS ($P = .001$)
Smeltzer and Lavietes[14]	4–10 (133)	Non-RCT	B	4 wk 1 session/wk 10 inspirations/10 expirations 90-s rest between repetitions	↑ P_{Imax} ($P = .001$) ↑ P_{Emax} ($P = .001$)	MS group: P_{Imax} 72.3% P_{Emax} 45.6% Control group: P_{Imax} 118.9% P_{Emax} 74.6%	Level of fatigue posttest ($P = .0001$)

(continued)

Table 2. RCTs on the Effectiveness of a Threshold Trainer in Respiratory Muscle Weakness Training of Patients With MS (continued)

Reference	PEDro Scale (n)	Type of Evidence	DR	Main Intervention	Intra-group Variables	Effect Size, Functional Variable	Effect Size, Clinical Variable
Ray[27]	5–10 (21)	Quasi-experimental trial	B	5 wk 3 d/wk 30 min/d	↑ P_{Imax} ($P < .001$)	P_{Imax} 23.91	Physical fatigue ($P = .02$) ↑ P_{Emax} ($P < .001$) P_{Emax} 23% FVC ($P = .052$) FVC 0.095% Cognitive fatigue ($P = .02$) Total fatigue ($P = .03$)
Bosnak-Guclu[15]	6–10 (73)	Case study	C	Maintained pressures for at least 1 s, with the highest measurement recorded	EDSS 0–2/2.5–4.5 group:	EDSS 0–2/2.5–4.5 group:	0 P_{Imax} 97.8/84.0 cm H_2O P_{Imax} 103.7/94.8 P_{Emax} 112.4/98.9 cm H_2O P_{Emax} 66.6/60.9 6MWT 582.2/446.4 m 6MWT 86/67.3 Healthy group: P_{Imax} 110.6 cm H_2O P_{Imax} 112.7% P_{Emax} 149.7 cm H_2O P_{Emax} 83.6% 6MWT 648.4 m 6MWT 98.1%
Foglio[16]	3–10 (24)	Case study	C	5 trials for at least 1 s, with the highest measurement recorded	P_{Imax} (r=0.50)	P_{Imax} 18–76 cm H_2O	G1 EDSS 5
				G1: performed the exercise test G2: did not perform the exercise test	P_{Emax} (r=0.55, $P < .01$)	P_{Emax} 16–82 cm H_2O	G2 EDSS 7
Buyse[17]	2–10 (60)	Case study	C	At least 3 trials, with the best performance used for analysis	P_{Imax} ($P < .002$) P_{Emax} ($P < .05$) ROMF P_{Imax} 38% ROMF P_{Emax} 22%	NLV P_{Emax} 37% NLV P_{Imax} 54%	EDSS mean value 6.5

* Calculated results for this table
DR = degrees of recommendation
RCT = randomized controlled trial
BEUEE = breathing-enhanced upper extremity exercises
P_{Imax} = maximum inspiratory pressure
P_{Emax} = maximum expiratory pressure
BS = Borg scale
EDSS = Kurtzke Expanded Disability Status Scale
PDI = pulmonary dysfunction index
6MWT = 6-min walk test
FSS = Fatigue Severity Scale
MVV = maximum voluntary ventilation
BAL = balance test
$FEF_{25-75\%}$ = forced expiratory flow during the middle half of the FVC maneuver
P1 = part 1 of the study
P2 = part 2 of the study
G1 = group 1
G2 = group 2

PI = pulmonary index
AMB = ambulatory patient
WB = wheelchair-bound patient
BR = bedridden patient
VC = vital capacity
RV = residual volume
TLC = total lung capacity
MIMS = maximum inspiratory muscle strength
MEMS = maximum expiratory muscle strength
SE = assessment session
PwMS = patients with multiple sclerosis
HC = healthy controls
DVRQLM = description of voice-related quality of life measure
ALSSS = amyotrophic lateral sclerosis severity scale
SVP = sustained vowel prolongation
MS = multiple sclerosis
NLV = normal lung volume
ROMF = restrictive or mixed function

summarize the levels of evidence and grades of recommendation of different therapeutic respiratory muscle training interventions with a threshold trainer in subjects with MS. Hence, the levels of evidence and grades of recommendation found for therapeutic interventions with a threshold trainer in patients with MS seem to be sufficient to recommend the interventions.

What Is the Evidence for Respiratory Muscle Training With a Threshold Trainer in Multiple Sclerosis Patients?

In this review, several studies on expiratory muscle and inspiratory muscle training have been included. Of these studies, we selected four in which patients received expiratory muscle training (one systematic review, 2 RCTs,
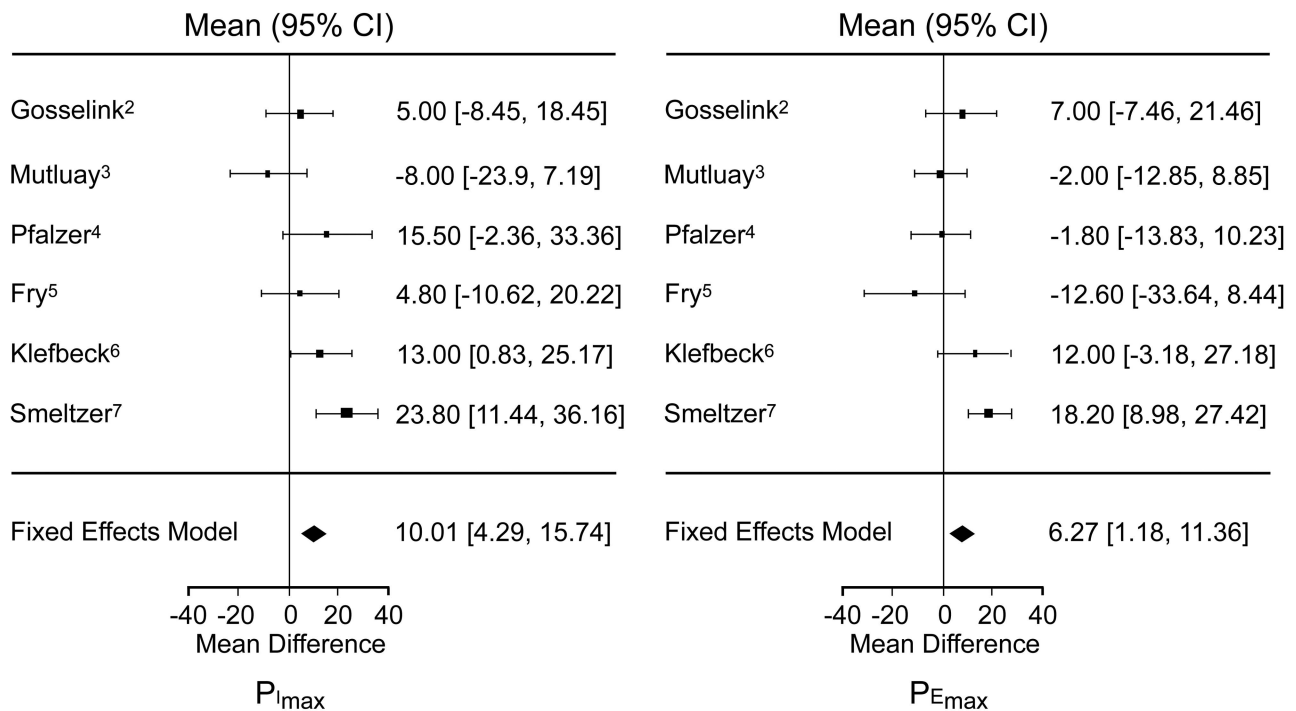
Fig. 1. Meta-analysis of data of randomized controlled trials. P_{Imax} = maximum inspiratory pressure. P_{Emax} = maximum expiratory pressure.

and one controlled clinical trial)[1,2,7,26] and three in which patients received inspiratory muscle training (3 RCTs),[4-6] the outcomes of which are detailed below. There also are other studies that show the relationship between the degree of disability and the impairment at both the physical and pulmonary function levels (2 systematic reviews, 3 study cases, one controlled clinical trial, and one RCT).[3,8,11,14-17] The studies are arranged according to the grade of recommendation.

The primary documents with a grade A recommendation showed clinical and functional changes that were statistically significant for most of the outcomes measured in each study. Only one study included a group of patients with MS for whom the degree of relationship between respiratory muscle weakness and state of health without therapeutic intervention was examined and another group in which the applied intervention was exhalation through a threshold trainer for 3 months at 7 d/week with 2 daily sessions consisting of 3 sets of 15 expirations per set at an intensity of 60% of P_{Emax}.[2]

The improvement in P_{Emax} was greater than the improvement in P_{Imax} at the end of the intervention. Significant changes were found in FVC ($P < .001$), P_{Imax} ($P < .01$), P_{Emax} ($P < .001$), the pulmonary dysfunction index ($P < .05$), and quality of life in comparison with the group that did not receive the therapeutic intervention.[2]

A previous study followed the same protocol with an intensity used in each expiration of 10% of P_{Emax}. Im-

provements in P_{Emax} were observed at the end of the therapeutic P_{Emax} intervention ($P < .003$).[7]

In another study with an A level evidence included in this review, it was proven that a series of exercises of the upper limb for 6 weeks at 30 min/day, along with controlled breathing, deep nasal inspiration and forced oral expiration, helped to achieve an increase in P_{Emax} ($P = .01$) and the pulmonary dysfunction index ($P = .002$).[3] In another review, P_{Emax} increases of 41 and 50% were found in a group of healthy people in training for 4 and 8 weeks, respectively.[11]

It has been established that a protocol of 10 weeks at a frequency of 7 d/week with 3 sets of 15 inspirations produced a significant improvement in P_{Imax} ($P = .003$[4] and $P < .001$),[5] whereas no significant improvements in P_{Emax} were observed. However, in other studies, improvements have been found in P_{Imax} ($P < .008$) but in smaller proportion in protocols of 10 weeks but at 2 sessions/day with 3 sets of 10 inspirations and 1 min of rest between sets. In addition to this, P_{Imax} was the only outcome in which the experimental group obtained a significant improvement.[6]

According to the studies included in this systematic review,[1-8,11,14-17,26] the training protocols in which the expirations are done in a specific way achieve greater results in P_{Emax}, and trials that focus on training respiratory muscles through inspirations obtain greater results in P_{Imax}.

In other outcomes studied in this review, it was observed that there was an improvement in FVC through

protocols of expiration at 60% P_{Emax},[2] whereas in exercise programs of the upper limb, the FVC did not show any improvement.[3] No data have been obtained for this outcome in inspiratory therapies; therefore, it would be interesting to investigate this aspect in future studies.

Another outcome is the Fatigue Severity Scale, which improves with protocols that did inspiration specifically (pretest value of 47.7, posttest value 46.3[4] and pretest value of 5.3, posttest value of 5.2[6]), although in research based on training inspirations, a stagnation of this value was detected (Fatigue Severity Scale 5.2).[5] In other studies, a decrease at the end of the Borg 6–20 rating of perceived exertion scale was observed, with an initial value of 15 and a final value of 14.5, thus improving by 3.2%,[3] and with a pretest value of 13 and a posttest value of 12.[6]

The studies showing grade B recommendations were rather heterogeneous. In the study by Smeltzer and Lavietes,[14] a group of patients and a group of healthy individuals both showed increases in P_{Emax} (45.6 and 74.6%, respectively) and P_{Imax} (72.3 and 118.9%, respectively). The quasi-experimental trial of Ray et al[27] also showed increases in P_{Imax} and P_{Emax} for training groups (23.9 and 23 cm H_2O, respectively), with initial values of 70 cm H_2O for P_{Imax} and 94 cm H_2O for P_{Emax}.[27] However, in the second study with grade B recommendations, no improvement was detected in the same outcomes at the end of a treatment carried out for 8 weeks at 5 days/week with 4 sets of 6 repetitions per day.[1] Unfortunately, very few studies had a large sample size in this systematic review. The sample size was 9–73 people, and only one study had a broader sample of 133 people. Thus, the lack of statistical difference in the study by Chiara et al[1] between the MS and control groups may have been due to the small sample size of participants.

The results showed no significant change in P_{Emax} or in sustained vowel prolongation and number of words/min ($P > .05$).[1] Similarly, in the review by Sapienza,[11] no scientific evidence was found to demonstrate the effectiveness of respiratory training with a threshold trainer in relation to improvement of speech and voice disorders.

With regard to coughing, it is assumed that the cough peak expiratory flow will increase if an expiratory strength training protocol increases the expiratory driving pressures. This increase will diminish the need to use vocal fold compression to generate an increased driving force during coughing. As a result, cough compression time will decrease.[26] As a result, there are no changes related to cough because there are not any significant changes in P_{Emax}.

The primary documents that have been studied with grade C recommendations showed features of patients included in the sample without any type of intervention other than analyzing the state of lung function, physical ability, and quality of life. They showed a clear relationship between the degree of disability and the impairment at both the physical and lung levels, so patients with lower EDSS scores reported minor levels of impairment compared with patients who had higher EDSS scores.[15-17]

The study by Foglio et al[16] showed a P_{Emax} range of 16–82 cm H_2O and a P_{Imax} range of 18–76 cm H_2O. Patients who were unable to perform the exercises reported a greater severity of the disease and less respiratory muscle strength, but there was no significant reduction in comparison with patients who were capable of doing the exercises.

Bosnak-Guclu et al[15] showed that patients with an EDSS score of 0–2 have lower values in terms of breathing capacity (P_{Imax} 97.8 cm H_2O [103.7%], P_{Emax} 112.4 cm H_2O [66.6%]) compared with patients with a score of 2.5–4.5 (P_{Imax} 84.0 cm H_2O [94.8%], P_{Emax} 98.9 cm H_2O [60.9%]), and both subgroups have lower values compared with the control group of healthy people (P_{Imax} 110.6 cm H_2O [112.7%], P_{Emax} 149.7 cm H_2O [83.6%]). This study was carried out to compare the functional exercise capacity, pulmonary function, and respiratory muscle strength of ambulatory MS patients with different disability levels against healthy controls, but the participants did not carry out respiratory muscle training, so it is not known if these patients would have improved after finishing respiratory muscle training.[15]

Bosnak-Guclu et al[15] also demonstrated the direct relationship between the severity of the disease and the results obtained in the 6MWT, observing the shortest distance traveled by those patients who obtained higher EDSS scores of 2.5–4.5 (446.4 m) in comparison with the group with the lowest EDSS scores of 0–2 (582.2 m) and with healthy subjects (648.4 m). Regarding the observed changes in the outcomes after the review, we found evidence that the 6MWT improved by over 13% (pretest value of 43, posttest value of 47) in the study by Mutluay et al[3] and by 12.3% (pretest value 293.9, posttest value 306.2) in the inspiratory program of Pfalzer and Fry.[4] Furthermore, the study by Buyse et al[17] showed a group with an EDSS score of < 7 and a group with an EDSS score of 7 or higher (P_{Imax} 50% of P_{Emax}, P_{Imax} 34, 36, and 26% of P_{Emax} average, respectively).

Primary documents with grade D recommendations were found not to be significant for this review.

Does the Choice of Inspiratory Muscle Strength or Endurance Training Matter?

A question to be taken into account in the planning of a respiratory muscle training protocol in patients with MS would be to determine which is more important: inspiratory muscle strength training or endurance training. Both types of training (strength and endurance) show a real improvement in muscle endurance, but only strength train-

ing is able to significantly improve P_{Imax}, P_{Emax}, and functional exercise capacity.

Many individuals with MS exhibit reduced respiratory muscle strength and endurance; this suggests that testing of respiratory muscle function should be routinely performed in this population.[1,5] Use of both inspiratory[5,6] and expiratory[1,2,14] muscle training improved respiratory muscle strength in patients with MS and should thus be included in the treatment of people who exhibit respiratory muscle weakness.

Muscle strength is measured mainly by P_{Imax} and P_{Emax}.[28] The majority of the studies included in this review had strength training as the main purpose. Two studies were focused on expiratory muscle training. One study showed no significant improvement in any P_{Emax} outcome ($P > .05$),[1] whereas Smeltzer et al[7] found that a significant improvement in P_{Emax} ($P = .003$) was obtained at the end of treatment based on expirations of 10% of P_{Emax}.

Sapienza[11] found improvements in P_{Emax} of 41% for a 4-week protocol and 50% for an 8-week protocol in a group of healthy people, whereas Gosselink et al[2] found improvements in both P_{Imax} ($P < .01$) and P_{Emax} ($P < .001$). In the study by Klefbeck and Hamrah Nedjad,[6] the protocol of inspiratory muscle training at 60% of P_{Imax} per session resulted in an increase in P_{Imax} ($P < .008$) and P_{Emax} ($P < .02$) and therefore an improvement in muscle strength. After examining the methods of strength training, it could be deduced that the treatments were based on repetition of very short sets several times daily.

There were only 2 studies in this review that included the 6MWT to test the physical capacity and endurance of the patient. Mutluay et al[3] conducted the 6MWT at the beginning and end of the protocol to determine if training with a threshold trainer had increased the strength of the respiratory muscles and the endurance of the patient, but the 6MWT is not a method of endurance training. The change in the outcome of the 6MWT at the end of the treatment was +13%. Similarly, in the study of inspiratory muscle training by Pfalzer and Fry,[4] the 6MWT was administered to determine if the endurance of the patient had increased after 10 weeks of training. The improvement in the 6MWT test was 12.3 m in the intervention group. According to these results, it follows that, in addition to increasing strength, respiratory muscle strength training also indirectly increases the endurance of the patient. It also increases the number of meters walked and therefore the physical capacity and quality of life of the patient.

Conclusion

To our knowledge, the majority of trials included in this review showed a unique protocol of inspirations or expirations. Therefore, it would be interesting to pursue new lines of research with a respiratory muscle training protocol in which both aspects work together and likewise to achieve an improvement in lung function and quality of life of patients with MS.

Further studies are required to advance and strengthen the existing scientific evidence, which is both limited and varied in its findings. We noted 2 limitations in the practical application of training by threshold trainers for patients with MS. First, researchers used samples of small sizes, which reduced the ability to detect the effects of treatment. In addition, studies were designed with a follow-up period that was not long enough, with 3 months as the longest protocol. Therefore, it would be interesting to extend the period to 6 or 12 months.

Finally, improvement was found in the force and endurance of breathing muscles during training programs that included the use of a threshold trainer as a way to treat muscle weakness. The 15 revised articles covered protocols of 10 weeks and 3 months carried out at a frequency of 7 days/week with one or 2 daily sessions consisting of 3 sets of 10 or 15 repetitions per set at an intensity of 10–60% of P_{Emax}.

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