Randomized Control Trial of Effects of a 10-Week Inspiratory Muscle Training Program on Measures of Pulmonary Function in Persons with Multiple Sclerosis

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Abstract: Pulmonary impairments have long been recognized as major causes of morbidity and mortality in individuals with advanced multiple sclerosis (MS). This study was designed to determine if a 10-week home exercise inspiratory training program in community-dwelling persons with MS improves pulmonary muscle strength and endurance. Forty-six ambulatory individuals with clinically diagnosed MS [Expanded Disability Status Scale (EDSS) 2.0–6.5, intervention group mean = 3.96 and control group mean = 3.36] were randomly assigned to an intervention group that received 10 weeks of inspiratory muscle strength training (IMT) or a nontreatment control group. Twenty-one subjects in the control group and 20 subjects in the intervention group completed the study. The intervention group demonstrated significantly greater improvement than the control group in maximal inspiratory pressure ($P < 0.001$). When compared to the control group, no significant differences were noted for maximal expiratory pressure or maximal ventilation volume after training in the intervention group. Baseline and postexercise training comparison of secondary pulmonary expiratory outcomes were significant in the intervention group for forced expiratory volume at one second (FEV_1) ($P = 0.014$), forced vital capacity (FVC) ($P = 0.041$), and midexpiratory flow rate ($FEF_{25–75\%}$) ($P = 0.011$). No significant changes were noted for the control group. Thus, IMT significantly increased inspiratory muscle strength and resulted in generalized improvements in expiratory pulmonary function in persons with MS who have minimal to moderate disability. Future studies are needed that focus on the long-term effects of IMT with increased resistance and the impact it has on increasing pulmonary function and functional performance.

Key words: *multiple sclerosis, pulmonary function tests, exercise, rehabilitation, respiration*

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INTRODUCTION

Multiple sclerosis (MS) is a primary disorder of the central nervous system that often affects motor pathways, causing diminished muscle strength and endurance throughout the body including the ventilatory muscles.[1–7] Respiratory complications are recognized as the major cause of morbidity and mortality in individuals with advanced MS.[1,2,8–11] Among those persons with MS who die before age 50, pneumonia and influenza are the cause of death in 20% of the cases.[11]

Pulmonary muscle weakness, especially expiratory muscle weakness, is common in persons with MS. The diaphragm, external intercostals, and accessory muscles of inspiration are often impaired in persons with neuromuscular disorders such as MS. Muscle weakness, muscle spasticity, muscle incoordination, and postural abnormalities contribute to impaired ventilatory function.[5] Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are indirect measures of inspiratory and expiratory pulmonary muscle strength respectively, and are defined as the pressure achieved with maximal forced inspiration or expiration. Studies of highly disabled persons with MS (Expanded Disability Status Scale [EDSS] score of >6.5) report MIP values ranging from 27% to 74% of predicted values and MEP values ranging from 18% to 51% of predicted values.[1,12–14] Fewer reports are available on pulmonary muscle strength in a less disabled MS population (EDSS ≤6.5). Reduced values of predicted MIP (mean ranging from 50%–77%) and MEP (mean ranging from 34%–60%) suggest significant pulmonary muscle weakness even in less disabled persons with MS.[4,14] Pulmonary muscle endurance is rarely reported. However, in the report by Smeltzer et al[15] on pulmonary function of 40 persons with MS disability ranging from ambulatory to bed-bound, mean maximal voluntary ventilation (MVV) values were only 68% of predicted values. MVV is an indirect measure of pulmonary muscle endurance, defined as the greatest amount of air an individual can breathe in and out in one minute.

It is reasonable to expect that patients with MS will benefit from specific inspiratory or expiratory muscle training. However, there is limited research reported on the efficacy of inspiratory muscle training (IMT) and expiratory muscle training in persons with MS. Pulmonary muscle

strength training is achieved through use of inexpensive hand-held devices that resist inspiration or expiration. Two studies have been reported utilizing resisted expiratory training in severely disabled persons with MS. In a study of 20 patients with EDSS scores of 6.5 to 9.5 (10 experimental and 10 control), Smeltzer et al[8] asked the experimental subjects to perform resisted expiratory exercises twice daily (three sets of 15 repetitions). Following three months of treatment, experimental subjects exhibited significantly greater MEP than the control group, but there was no significant group difference for MIP. Similarly, Gosselink et al,[1] in a study of 18 patients with EDSS scores of 7.0 to 9.5 (nine experimental and nine control), used expiratory muscle training and found trends toward increased MEP and MIP, but the increases did not reach significance. In the only study on persons with mild to moderate disability due to MS (EDSS scores of 1.5–6.5), Chiara et al[16] conducted eight weeks of expiratory muscle training five days per week for 17 subjects with MS and 14 non-MS control subjects. They found significant increases in MEP and peak expiratory flow in their MS group.

The only published study of resisted IMT in persons with MS was reported by Klefbeck et al[13] using 15 patients with EDSS scores of 6.5 to 9.0 (seven experimental and eight control). Subjects completed three sets of 10 repetitions of resisted inspiration twice every other day for a period of 10 weeks. Experimental subjects exhibited significant increases in both MIP and MEP that were maintained one month after completion of the training. When compared to the control group, only the MIP was significantly better in the experimental group. To date, no studies have been reported on IMT in less disabled persons with MS. Nor have any of the pulmonary training studies in persons with MS reported changes in pulmonary muscle endurance as measured by MVV.

The purpose of this study was to determine if a 10-week IMT program in ambulatory persons with MS would increase pulmonary muscle strength as measured by MIP and MEP, and pulmonary muscle endurance as measured by MVV.

METHODS

Participants

Ambulatory subjects (with/without assistive devices) with clinically diagnosed MS who were 18 years of age or older were recruited to participate in the study. Based on medical history, people were excluded from participation in the study if they had: an acute respiratory infection as diagnosed by a physician, oral temperature >100° F, unstable cardiopulmonary/musculoskeletal conditions unrelated to MS affecting performance, or current smoking history.

Researchers recruited subjects through a television interview on a local news station, as well as personal solicitation at local MS support group meetings. Forty-six individuals met the inclusionary criteria and participated in the study [23 intervention training group (I) (female = 21, male = 2); 23 control group (C) (female = 17, male = 6)]. Of the 46 subjects who participated in the pretest session, two withdrew due to illness unrelated to a neurologic exacerbation and three subjects no longer wished to participate in the study. Twenty-one subjects in the C group and twenty subjects in the I group completed the study. Mean age (SD, range) was 50.0 (9.1, 35–69) for the I group and 46.2 (9.4, 23–64) for the C group. Mean height (SD, range) was 1.7 m (0.1, 1.5–1.8) for the I group and 1.7 m for the C group (0.1, 1.4–1.9). Mean EDSS (SD, range) was 3.96 (1.80, 2.00–6.50) for the I group and 3.36 (1.47, 2.00–6.50) for the C group. Subjects in the I group had the following types of MS: relapsing remitting (10), secondary progressive (three), primary progressive (four), and progressive relapsing (two). Subjects in the C group had the following types of MS: relapsing remitting (16), secondary progressive (four), primary progressive (one), and progressive relapsing (one).

Participants were randomly placed into a home exercise I group or C group by date of enrollment in the study. Subjects completed a Health Intake Questionnaire which included basic demographics and information about their MS diagnosis. To ensure participant safety, resting vital signs of blood pressure, oxygen saturation, heart rate, respiratory rate, and oral temperature were assessed using the guidelines of the American College of Sports Medicine (2002) prior to activity.[17] Exercise participation was determined to be safe for all participants.

This study was approved by the Institutional Review Board of the University of Michigan-Flint and informed consent was obtained from all subjects prior to participation in the study. All subjects were provided with a pamphlet on principles of healthy living and an additional incentive of a free recreation center pass at the university upon completion of the study.

MS Disability Classification

Disability level was determined using EDSS, a scale developed specifically for the MS population and based on the Kurtzke Functional Systems Scores (FSS) and the subject's ambulatory status. Tests of pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral function are included in the FSS. Higher scores on the EDSS indicate greater disability with scores greater than 6.5 indicating the person can no longer ambulate beyond five meters even with physical assistance.[18]

Fatigue was measured by the Fatigue Severity Scale (FatigueSS), a nine-item questionnaire addressing fatigue during activities of daily living (ADL) with each item scored on a seven-point Likert scale (1 = strong disagreement and 7 = strong agreement). This test was developed by Krupp et al[19] specifically to measure levels of fatigue in patient populations where fatigue is a primary characteristic such as MS. The FatigueSS has high internal consistency, test-retest reliability ($r = 0.84$), and sensitivity in the MS population.

Pulmonary Function Tests

The investigator who conducted the prepulmonary and postpulmonary function tests was blinded to group assignment. Pulmonary tests were conducted with the VMax metabolic cart and test protocols from Sensor Medics Corporation (22705 Savi Ranch Parkway, Yorba Linda, CA 92687-4609) (Figure 1). The metabolic cart was calibrated prior to each test session according to the American Thoracic Society and European Respiratory Society Statement on Respiratory Muscle Testing, and the VMax pulmonary test software has

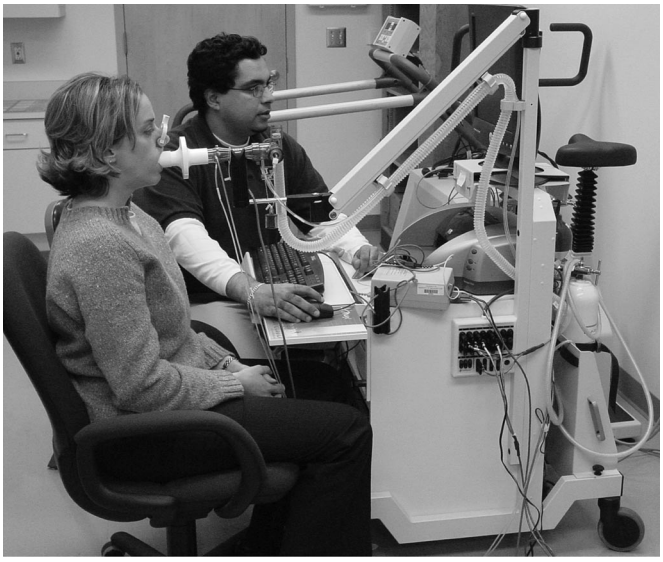

FIGURE 1. Subject positioning and equipment for pulmonary function tests.

routine measures of consistency and accuracy imbedded in the test protocol.[20] Pulmonary tests were performed in the following order each test session: flow volume loop test, total lung capacity test, minute ventilation test, maximal inspiration and expiration test, MIP/MEP, and MVV. Verbal instructions were provided followed by a videotaped demonstration of each test procedure. To ensure reproducibility, each test was performed in a standardized position a minimum of two times and until values were within 10% of each other with the best trial accepted. Rest periods were provided as requested by subjects throughout testing to minimize fatigue.

Pulmonary Disorder Classification

Subjects were classified based on presence of pulmonary disorders defined as a restrictive disorder, obstructive disorder, or combined disorder, determined from the results of standard spirometry measures that included: vital capacity (VC), forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), forced midexpiratory flow ($FEF_{25–75\%}$), and peak expiratory flow (PEF).[10,21] VC is the volume change at the mouth between the position of full inspiration and complete expiration. FVC is the maximal volume of air exhaled with maximally forced effort from a maximal inspiration. FEV_1 is the volume of air exhaled in the first second of a forced expiration from a position of full inspiration. $FEF_{25–75\%,}$, the mean forced expiratory flow between 25% and 75% of the FVC (also labeled midexpiratory flow), is considered a more sensitive indicator of obstructive impairment as compared to PEF. PEF is the maximum expiratory flow achieved from a maximum forced expiration, starting without hesitation from the point of maximal lung inflation.[22] Subjects were classified based on their level of pulmonary pathology and impairment.

Pulmonary disorder refers to characteristics of obstructive (air trapped in the lungs) or restrictive (not enough air entering the lungs) disorders. The criteria for classification of obstructive disorder was when FEV_1 /FVC or $FEF_{25–75\%}$ was less than 75% of predicted values.[20,21] The criteria for classification of restrictive disorder was when FVC was less than 75% of predicted values.[10,23] Subjects received the classification of combined obstructive and restrictive disorder if they met both of the criteria.

Pulmonary Impairment Classification

Subjects were classified as having impaired inspiratory or expiratory muscle strength if MIP or MEP, respectively, were less than 60% of predicted values.[20] Subjects received the classification of both inspiratory and expiratory muscle weakness if they met the criteria for both MIP and MEP. Subjects were classified as having impaired pulmonary endurance if MVV was less than 75% of predicted values.[20]

Pulmonary Home Exercise Intervention

Subjects in the experimental group were given a Threshold Inspiratory Muscle Trainer (IMT) device shown in Figure 2 (Respironics Health Scan, Inc., 41 Canfield Road, Cedar Grove, NJ, 07009). The investigators provided instruction on proper technique to the subjects in the I group and subjects practiced with investigators until proper technique was demonstrated. The home IMT resistive exercise intervention, presented in Table 1, was based on previously published protocols.[8,13] Subjects ranked their perception of fatigue during IMT training using a Borg Rating of Perceived Exertion (RPE)[24] Scale. Subjects also completed a log documenting exercise adherence, Borg RPE, and symptoms following the daily exercise sessions. All subjects tolerated the exercise training program except for one subject who complained of lightheadedness during the initial training session. To resolve the light-headedness for this subject, pressure resistance was reduced by 2 cm H_2O.

Compliance with IMT Training

Subjects in the IMT group were classified into one of four categories of weekly compliance with the IMT protocol. This was based on the percent of required sets and repetitions

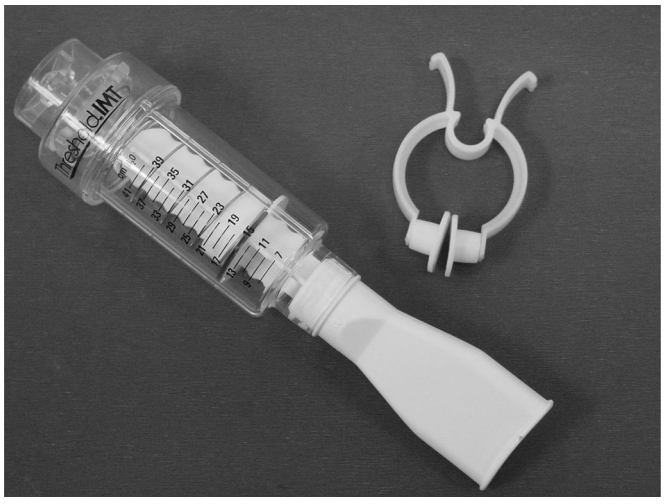

FIGURE 2. Inspiratory muscle threshold trainer.

TABLE 1. Ten-Week Home IMT Exercise Training Protocol
Frequency: IMT exercises performed daily for 10 weeks.
Overload: Repetitions and Sets: Three sets of 15 repetitions*
Resistance: Initial resistance (H_2O cm) of the IMT was set at 30% of the subjects pretest MIP.
Progression: Subjects were called once per week by one of the investigators to assist with IMT pressure resistance training progression. IMT pressure resistance was progressed weekly according to the subject's baseline MIP pressure and RPE as well as the subject's symptoms

Subject's Baseline MIP Pressure: <50 cm H_2O				
Borg RPE	**<13**	**13 to 15**	**>15**	**>17**
Pressure resistance (cm H_2O)	Increased by 2	Increased by 1	Maintained at same level	Reduced by 2
Subject's Baseline MIP pressure: >50 cm H_2O				
Borg RPE	**<13**	**13 to 15**	**>15**	**>17**
Pressure resistance (cm H_2O)	Increased by 4	Increased by 2	Maintained at same level	Reduced by 2
If subjects developed symptoms (ie, dizziness, lightheadedness, or shortness of breath) while performing IMT exercises, the resistance was adjusted as follows until no symptoms persisted.				
Symptoms	Two or more symptomatic episodes in a row per week		1–2 isolated symptomatic episodes per week	
Pressure resistance (cm H_2O)	Decreased by 2 subjects were called back 3 days later to monitor subject's response		Held constant, subjects were called back 3 days later to monitor subject's response	

* If a subject achieved the maximum IMT Trainer pressure resistance of 41 cm H_2O and resistance could no longer be increased, a fourth set of exercises was added along with an increased number of repetitions up to a maximum of 15 repetitions.
Abbreviations: IMT, inspiratory muscle strength training; MIP, maximal inspiratory pressure; RPE, rating of perceived exertion.

of the exercise program they completed: (1) fully compliant if 85% were completed, (2) partially compliant if 70% to 84% were completed, (3) poorly compliant if 50% to 69% were completed, and (4) noncompliant if 10% to 49% were completed.

Control Group Interaction

Subjects in the C group were called at four, eight, and 10 weeks to report complications such as an exacerbation or pulmonary infection, and to check for changes in level of physical activity during the 10-week study period. Upon completion of posttests, subjects in the C group were provided an IMT with instructions on safe IMT use and resistance progression along with an offer to answer any further questions by telephone.

Posttesting

All subjects were retested for pulmonary function and Fatigue following the 10-week home exercise intervention.

Data Analysis

Statistical analyses were completed with SPSS for Windows, version 10.2. Descriptive statistics (mean, SD) were calculated for all subject characteristics and the following pulmonary variables: MIP, MEP, FVC, FEV_1, FEV_1/FVC, MVV, $FEF_{25–75\%}$, PEF, and VC. Frequency counts and percentages were calculated for the FSS item scores to more fully describe the research subjects. FSS item scores of 0 to 1 were classified as normal/minimal impairment and FSS item scores of 2 or more were classified as moderate/severe impairment with disability. Nonparametric Spearman Rho correlations were used to compare the relationship between the FSS item scores and the primary pulmonary outcome variables.

All variables had homogeneity of variance and demonstrated a normal distribution. To determine effectiveness of the subject randomization process, baseline data were compared between groups with a one-way analysis of variance (ANOVA) for interval scale outcome measures and with a nonparametric Mann-Whitney U test for the EDSS scores ($P < 0.05$).

To determine the effect of the 10-week IMT home exercise intervention with multiple outcomes (MIP, MEP, and MVV), a multivariate analysis of variance of group (MANOVA, type IV full factorial model with simple contrast with alpha level = 0.05) using change scores (Posttest—Pretest measures) of MIP, MEP, and MVV was conducted to account for initial group differences. The MANOVA minimizes false-positive results when analyzing several outcome measures. Prior to conducting the MANOVA, the assumptions for the MANOVA were tested and met. One-way repeated measures ANOVAs were conducted on all outcomes measures (type IV full factorial model with simple contrast with alpha level = 0.05).

RESULTS

Sample Characteristics

There were no statistically significant differences between the C and I groups prior to intervention on subject characteristics (age, height, EDSS, total FatigueSS score, number of comorbidities, and total number of medications)

indicating that overall randomization of subjects was effective.

MS-Related Impairment/Disability

Subjects' EDSS scores ranged from 2.0 to 6.5 indicating minimal to moderate disease severity and disability. For the pyramidal function item of the FSS, only one control subject scored a 4 (marked paraparesis or hemiparesis) and no subjects scored a 5 (paraplegia, hemiplegia, or marked quadraparesis). No subjects scored a 4 on brainstem function of the FSS (marked dysarthria or other marked disability). Only one I subject scored a 5 (unable to perform coordinated movements due to ataxia) and no others subjects scored a 4 (severe ataxia in all limbs—most function is very difficult) on the cerebellar function item of the FSS.

Baseline impairment/disability levels of subjects on individual FSS items were relatively low with the exception of the sensory and cerebral function items as shown in Table 2. Spearman Rho correlations between FSS items and pulmonary muscle strength (MIP and MEP) and endurance (MVV) were nonsignificant with the exception of a low, but significant correlation between MVV and cerebellar function ($r = -0.296$, $P = 0.048$). Both MVV and MEP showed low, but significant correlation with the EDSS ($r = -0.356$, $P = 0.016$ and $r = -0.329$, $P = 0.028$, respectively).

Comparison of Baseline Data

Descriptive statistics for each group's baseline and postintervention actual and predicted pulmonary measures are shown in Tables 3 and 4. There were no statistically significant differences between the C and I groups on pretest for most of the predicted pulmonary values based on the subject's age, height, and sex. However, predicted MIP ($P = 0.021$) and $FEF_{25-75\%}$ ($P = 0.003$) were significantly different between the C group and I group on pretest, with the I group showing significantly lower means than the C group.

Pulmonary Impairment Classification

Subjects' pulmonary impairments, before and after intervention, are shown in Table 5. During pretesting 27 subjects (60.0%) demonstrated inspiratory muscle impairment and 29 subjects (64.4%) demonstrated expiratory muscle impairment. Twenty-one subjects (46.7%) had both inspiratory and expiratory muscle strength impairment (decreased MIP and MEP). Eleven of 23 subjects (47.8%) in the C group and 16 of 23 subjects (69.6%) in the I group were initially classified with an inspiratory muscle strength impairment (MIP <60% of predicted). After the intervention, one of 20 subjects (5.0%) in the I group and four of 20 subjects (20.0%) in the C group had inspiratory muscle strength impairment (MIP <60% of predicted), while expiratory muscle strength impairments (MEP <60% of predicted), and muscle endurance impairment (MVV <75% of predicted) were essentially unchanged. This resulted in far fewer subjects demonstrating both inspiratory and expiratory muscle strength impairment after the intervention.

Pulmonary Disorder Classification

Table 6 shows the pulmonary disorder classification of subjects as obstructive, restrictive, or both. At baseline, 20 (43.5%) out of 46 subjects were classified as having obstructive disease (decreased FEV_1/FVC or $FEF_{25-75\%}$) [I = 12 (52.2%), C = 8(34.8%)]. Only one subject (2.2%) in the C group and no I group subjects demonstrated restrictive disease (decreased FVC) characteristics.

Comparisons Following Intervention

Adherence to the IMT training protocol averaged 81% (SD = 6.93) for the I group for the entire study duration ranging from 76.25% to 83.50%. MANOVA results for group effects reported in Table 7 were significant indicating that the 10-week home IMT resistive exercise training intervention was effective at increasing MIP in the I group as compared to the C group. Figure 3 demonstrates the improvement in MIP made by the subjects in the I group before and after intervention as compared to the C group. The results of the

TABLE 2. Kurtzke Functional Systems Scores at Pretest for All Subject ($n = 46$)

FSS Item	Normal Score or Minimal Impairment (FSS = 0–1)	Moderate to Severe Impairment with Disability (FSS ≥2)	Correlation with MIP*	Correlation with MEP*	Correlation with MVV*
Pyramidal function	93.5%	6.6%	−0.118	−0.116	−0.178
Cerebellar function	77.8%	21.8%	−0.261	−0.291	−0.296†
Brainstem function	91.0%	8.7%	−0.006	−0.059	−0.154
Sensory function	17.3%	82.6%	0.078	−0.094	0.032
Bowel and bladder function	63.0%	36.9%	−0.034	−0.008	0.095
Visual function	76.1%	23.9%	−0.233	−0.273	−0.155
Cerebral (or mental) function	26.1%	73.9%	0.012	0.048	0.097
Other function	82.6%	17.4%	−0.158	−0.270	−0.168
EDSS			−0.275	−0.329†	−0.356†

* FSS item correlations are Spearman Rho; EDSS correlations are Pearson Product Moment.

† Significant at $P < 0.05$

Abbreviations: FSS, functional systems score; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; MVV, maximal voluntary ventilation; EDSS, Expanded Disability Status Scale.

TABLE 3. Descriptive Statistics for Predicted Percents of MIP, MEP, MVV, and FatigueSS

		Pretest (n = 46, 23 each group)		Posttest			
	Group	Mean	SD	Mean	SD	Percent Change (%)	*P* value
MIP	Intervention	53.1	25.7	76.6	23.3	80.9	<0.001
	Control	72.5	28.1	71.8	27.0	2.6	
Predicted MIP (%)	Intervention	53.4	25.4	94.0	30.3		<0.001
	Control	72.6	28.2	77.9	25.5		
MEP	Intervention	68.7	27.1	73.2	22.7	21.4	0.291
	Control	89.4	47.0	85.8	46.2	5.6	
Predicted MEP (%)	Intervention	46.4	19.1	49.2	16.6		0.355
	Control	52.6	21.0	50.1	21.1		
MVV[c]	Intervention	93.3	21.4	98.3	22.8	9.0	0.101
	Control	111.9	31.6	110.9	37.7	−1.5	
Predicted MVV (%)	Intervention	90.5	18.9	94.5	20.4		0.062
	Control	94.7	18.5	92.2	21.2		
FatigueSS	Intervention	5.2	1.1	5.2	1.2		0.961
	Control	5.6	1.2	5.3	1.3		

Abbreviations: FatigueSS = Fatigue Severity Scale (item averages); MIP = Maximal Inspiratory Pressure (cm of water); MEP = Maximal Expiratory Pressure (cm of water); MVV = Maximal Voluntary Ventilation (l/min).

TABLE 4. Descriptive Statistics for Predicted Percents of Pulmonary Function Measures

		Pretest (n = 46, 23 each group)		Posttest (Control = 21, Intervention = 20)			
	Group	Mean	SD	Mean	SD	Percent Change (%)	*P* value
FVC	Intervention	3.53	0.75	3.73	0.73	4.2	0.040
	Control	3.99	1.02	4.00	1.05	−1.8	
Predicted FVC (%)	Intervention	101.4	17.1	107.0	13.7		0.044
	Control	103.1	18.0	101.7	17.6		
FEV_1	Intervention	2.54	0.63	2.77	0.54	8.8	0.010
	Control	3.09	0.69	3.00	0.79	−4.9	
Predicted FEV_1 (%)	Intervention	103.1	18.0	101.7	17.6		0.002
	Control	104.1	18.6	99.1	17.4		
FEV_1/FVC	Intervention	.724	.118	.748	.079		0.058
	Control	.782	.078	.765	.095		
Predicted FEV_1/FVC	Intervention	.950	.149	.990	.104		0.016
	Control	1.01	.010	.982	.123		
$FEF_{25–75\%}$	Intervention	2.16	0.79	2.39	0.87	10.5	0.020
	Control	3.02	0.86	2.86	1.08	−12.9	
Predicted $FEF_{25–75\%}$	Intervention	72.0	23.1	80.3	26.1		0.010
	Control	92.6	21.9	87.0	25.4		
VC	Intervention	3.64	0.72	3.80	0.75	3.1	0.009
	Control	4.12	1.03	4.02	1.06	−3.6	
Predicted VC (%)	Intervention	104.2	16.3	109.0	14.5		0.011
	Control	106.6	16.7	103.4	17.0		

Abbreviations: $FEF_{25–75\%}$ = Forced Expiratory Flow (l/sec); FEV_1 = Forced Expiratory Volume at 1 second (l/sec); FVC = Forced Vital Capacity (l/min); VC = Vital Capacity(l/min).

repeated measures ANOVAs of MVV ($P = 0.101$) and MEP ($P = 0.291$) to determine significant between group differences postintervention were not significant at $P < 0.05$. Secondary analyses with the nonparametric, Mann-Whitney *U* test were conducted due to low power of these variables and were not significant.

For the I group compared to C group, repeated measures ANOVAs of baseline to postintervention data yielded

TABLE 5. Pulmonary Inspiratory and Expiratory Impairment Classification*

Impaired Ventilatory Muscle Strength

	Pretest (n = 45)						Posttest (n = 41)					
	Inspiratory		Expiratory		Both		Inspiratory		Expiratory		Both	
Groups	%	n	%	n	%	n	%	n	%	n	%	n
Control	50.0	11	54.5	12	36.4	8	20.0	4	60.0	12	10.0	2
Intervention	69.6	16	74.9	17	56.5	13	5.0	1	80.0	16	5.0	1
Both groups	60.0	27	64.4	29	46.7	21						

Impaired Ventilatory Muscle Endurance

	Pretest (n = 46)				Posttest (n = 41)			
	Normal		Impaired		Normal		Impaired	
Group	n	%	n	%	n	%	n	%	n
Control	23	78.3	18	21.7	5	80.0	16	20.0	4
Intervention	23	82.6	19	17.4	4	85.0	17	15.0	3
Both groups	46	80.4	37	19.6	9				

* Maximal inspiratory pressure and maximal expiratory pressure classified as impaired when <60%; maximal voluntary ventilation classified as impaired when <75%.

TABLE 6. Pulmonary Disorders Classification

Pulmonary Disorders

	Pretest (n = 46)							Posttest (n = 41)					
	Obstructive		Restrictive		Both			Obstructive		Restrictive		Both	
Group	n	%	n	%	n	%	n	n	%	n	%	n	%	n
Control	23	34.8	8	4.3	1	0	0	21	28.6	6	4.8	1	0	0
Intervention	23	52.2	12	0	0	0	0	20	40	8	0	0	0	0
Both groups	46	43.5	20	2.2	1	0	0	41						

TABLE 7. Respiratory Muscle Strength and Endurance MANOVA Between Subjects Effects

Dependent Variable	Type IV Sum of Squares	df	Mean Square	F	Sig.	Observed Power
MIP change	6309.642	1	6309.642	21.013	<0.001	0.994
MEP change	436.703	1	436.703	1.146	0.291	0.181
MVV change	574.543	1	574.543	2.326	0.136	0.318

Abbreviations: MEP = Maximal Expiratory Pressure (cm of water); MIP = Maximal Inspiratory Pressure (cm of water); MVV = Maximal Voluntary Ventilation (l/min).

significant increases for FEV_1 ($P = 0.002$), FVC ($P = 0.040$), and $FEF_{25–75\%}$ ($P = 0.020$). None of the C group comparisons were significant. Figure 4 illustrates the improvement made by the subjects in the I group before and after intervention as compared to the C group for pulmonary function. Nonspecific or generalized improvements in expiratory pulmonary function are indicated by the improved FEV_1, FVC, and $FEF_{25–75\%}$ percent change values for the I group while the C group had diminished values as shown in Table 4.

No significant change was noted in the FatigueSS scores for either the I or C groups. Baseline mean (SD) scores for the I and C groups were 5.2 (1.1) and 5.6 (1.2) respectively out of a seven-point score indicating severe complaints of fatigue. The FatigueSS scores for both groups following intervention were 5.2 (1.2) and 5.3 (1.3), respectively.

DISCUSSION

Pulmonary Function Status Compared with Other Studies

Our baseline data confirm previous findings that MIP, MEP, and $FEF_{25–75\%}$, in persons with MS who exhibit minimal to moderate disability (EDSS ≤6.5), are well below the predicted normal pulmonary function level (Tables 3 and 4).[4,6,7,14] During pretesting 27 subjects (60.0%), 11 of 23 subjects in the C group and 16 of 23 subjects in the I group, were initially classified with an inspiratory muscle strength impairment (MIP <60% of predicted) and 29 subjects (64.4%), demonstrated expiratory muscle impairment (Table 5). Twenty-one subjects (46.7%) had both inspiratory and expiratory muscle strength impairment (decreased MIP and MEP).

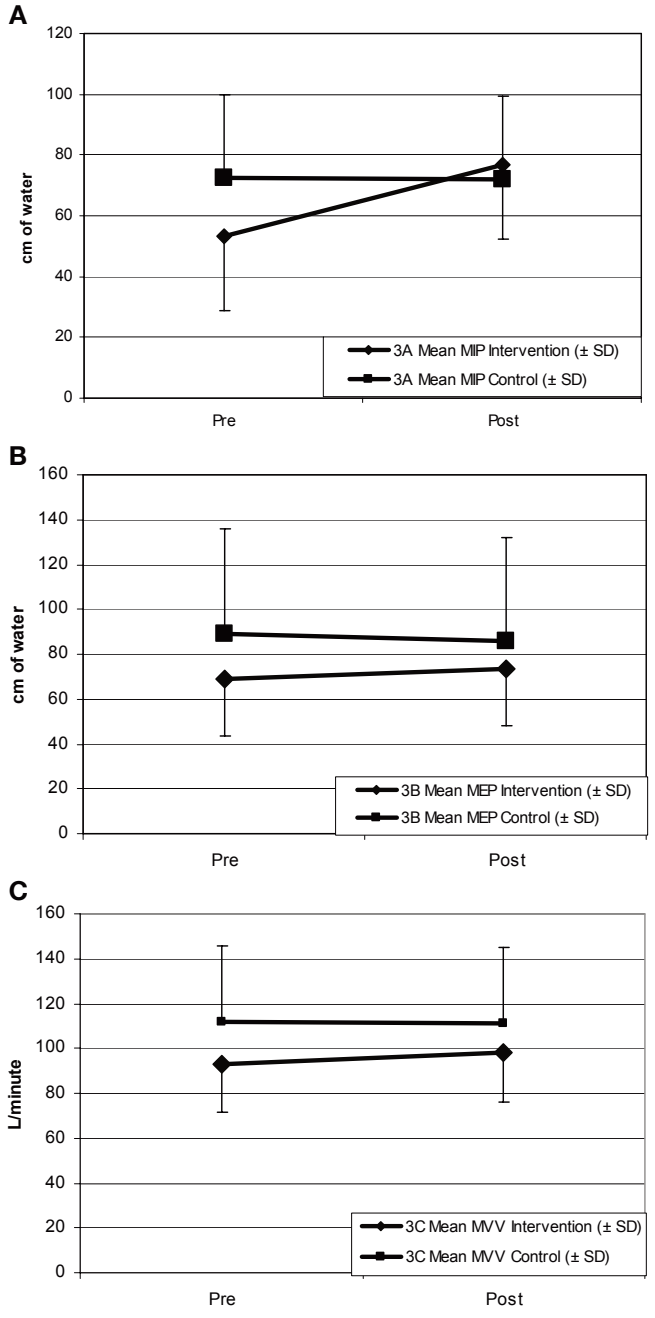

FIGURE 3. A. Average maximal inspiratory pressures for the intervention group and control group before and after intervention. B. Average maximal expiratory pressures for the intervention group and control group before and after intervention. C. Average maximal voluntary ventilation (MVV) for the intervention group and control group before and after intervention.

Effect of IMT on Inspiration, Expiration, and Muscle Strength Impairment

Resisted pulmonary exercise reduces pulmonary impairment in people with MS with minimal to moderate disability (EDSS <6.5). Specifically, this study demonstrates that a home exercise program of IMT reduces inspiratory muscle impairment and increases inspiratory muscle strength as measured by MIP. Following the 10-week IMT intervention, the I group had an 81% improvement in inspiratory muscle strength as measured by MIP (Table 3).

The significant improvements in our study for MIP (81%) were achieved by subjects who have MS with minimal to moderate disability (EDSS mean score for I group = 3.96) following IMT. While other controlled studies on IMT in less disabled persons with MS have not been published, this finding is consistent with the recently published work by Chiara et al[16] who documented a significant increase in MEP following expiratory muscle training in less disabled persons with MS. The three published controlled studies on pulmonary exercise interventions for more disabled persons with MS (EDSS scores of >6.5 or who were wheelchair-bound or bed-ridden) utilized small samples (no greater than 18 subjects per study) and found improvement in the respiratory function trained.[1,8,13] Thus, initial research evidence supports the use of resisted inspiratory and expiratory exercise to improve pulmonary function in both less and more disabled persons with MS. Additional research with larger studies needs to be conducted to confirm these initial findings.

Subjects were classified as having impaired inspiratory or expiratory muscle strength if MIP or MEP, respectively, were less than 60% of predicted values.[20] The IMT had a beneficial effect on reducing frequency of inspiratory muscle strength impairment. Only one of 20 subjects (5.0%) in the I group remained impaired from the initial 16 of 23 subjects (69.6%) in the I group classified as impaired at baseline (Table 5). A reduction in inspiratory muscle strength impairment also occurred in the C group, but the reduction was much less with four of 20 subjects (20.0%) in the C group classified as impaired at posttest compared to 11 of 23 subjects (47.8%) at baseline (Table 5). There was a greater amount of variability in the MIP, MEP, and MVVs of the C group as compared to the I group, which explains the shift toward less inspiratory muscle impairment of individuals in the C group at posttest. In the C group at posttest, nine subjects increased their MIP while 10 subjects decreased their MIP and one subject remained unchanged. These changes in MIP resulted in fewer C group subjects' classification as impaired at posttest.

Pulmonary expiratory muscle strength, as measured by MEP, improved 21% in the I group, however this increase was not significant due to the large standard deviations for MEP and low power (0.181). MVV changed in a positive direction yet was not significant ($P = 0.101$) with low power (0.318), while predicted MVV neared significance ($P = 0.062$). These findings are consistent with a previous report by Klefbeck et al,[13] where within group comparisons showed an increase in both MIP and MEP following inspiratory training, whereas only MIP showed significant improvement when compared to the control group. The greater percent improvement in inspiratory muscle strength in our study (81%) compared to the Klefbeck et al study[13] (approximately 50% at 10 weeks) may be explained by the: (1) larger number of subjects in our study, (2) difference in MS-related disability level between the subjects in each study, and (3) slightly

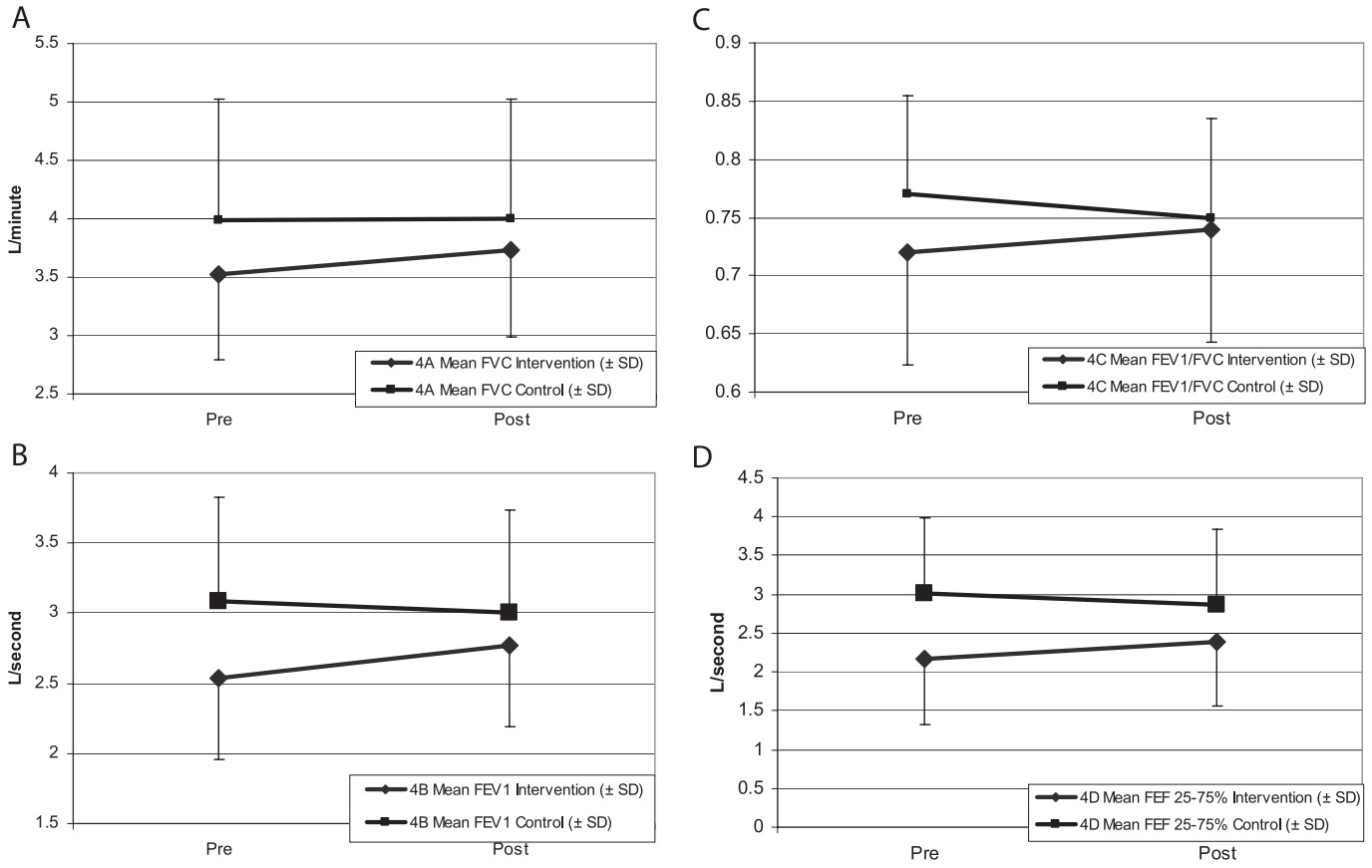

FIGURE 4. A. Average force vital capacity (FVC) for the intervention group and control group before and after intervention. B. Average force expiratory volume at 1 second (FEV_1) for the intervention group and control group before and after intervention. C. Average forced expiratory volume (FEV_1)/forced vital capacity (FVC) ratio for the intervention group and control group before and after intervention. D. Average forced midexpiratory ($FEF_{25–75\%}$) flow for the intervention group and control group before and after intervention.

higher baseline pulmonary function that allowed our subjects to train at a higher overload with daily training, weekly advancement of the overload, and training at a higher resistance.

Effect of IMT on Pulmonary Disorders

FVC, FEV_1, FEV_1/FVC, and $FEF_{25–75\%}$ were statistically significant for between groups differences after intervention (Table 4). Group mean data consistently reflected improved pulmonary function for the I group and decreased pulmonary function for the C group for all of these pulmonary function measures. Subjects' improved ability to take a deep breath in appears to have improved the subjects' expiratory volumes. This may be considered clinically important and further substantiates the indirect positive effects of IMT on expiratory pulmonary function. The inspiratory training overload resulted in nonspecific or generalized improvements in expiratory pulmonary function as shown by percent increases in FEV_1 and $FEF_{25–75\%}$ in Table 4.

We found that 43.5% ($n = 20$) of subjects at baseline were classified as having an obstructive disease pattern (FEV_1/FVC or $FEF_{25–75\%}$ <75% of predicted values). Only one subject demonstrated restrictive disease pattern (FVC < 75% of predicted values) (Table 6). Eight of the 12 subjects in the I group ($n = 23$) initially classified with a disorder remained impaired following intervention (Table 6). Grasso et al[25] classified subjects as having a pulmonary disorder if their test values were less than 80% of predicted values, though classification into obstructive and restrictive categories was not reported. They found pulmonary disorders in 35.7% of ambulatory subjects with MS. Thus, even with the more conservative method of classification used in our study, we found a greater percentage of ambulatory persons with MS who exhibited pulmonary disorders. The subjects' pulmonary disorders were a direct result of their neuromuscular disease or deconditioning since potential subjects were excluded from participation in the study if they were current smokers, had an acute respiratory infection as diagnosed by a physician, had an oral temperature >100° F, or had unstable cardiopulmonary/musculoskeletal conditions unrelated to MS which would affect their pulmonary performance. The obstructive nature of the pulmonary disorders observed in our subjects may be attributed to: (1) previous history of smoking

(our study included subjects with a prior history of smoking even though none were current smokers), or (2) possible pulmonary infections causing fibrosis of the lungs.[26]

Pulmonary Function Related to Neurologic Function

Previous authors have suggested that pulmonary impairments in persons with MS may be due to cerebellar involvement,[25] bulbar involvement affecting laryngeal and pharyngeal function,[5] and/or tonal and strength changes in muscles involved in respiration,[15] though little empirical evidence is available. In a cursory attempt to determine if there is a relationship between function of the central nervous system and pulmonary function, we examined the relationship between item scores on the FSS and our primary pulmonary outcome variables.[18] Individual FSS item scores ranged from 0 to 5, however, as shown in Table 2, less than 25% of subjects demonstrated scores of 2 or greater (with the exception of sensation, cerebral function, and bowel and bladder function) indicating low rates of impairment and disability. Spearman Rho correlations computed the relationship between pulmonary function and FSS items and ranged from 0.006 to 0.296 indicating little or no association between the FSS individual items and subjects' MIP, MEP, and MVV. This cursory examination of this relationship does not rule out, however, that if using other testing methods of neurologic function, a relationship between specific central nervous system dysfunction and pulmonary function may be found.

Pearson Product Moment correlations of EDSS scores with MEP and MVV revealed low, but significant correlations. In a similar population of subjects Mutluay et al[4] also found a weak, but significant correlation of EDSS with MEP, whereas Savci et al[7] found even lower, nonsignificant correlations between EDSS and MIP and MEP. Gosselink et al[1] found high correlations of the EDSS and MEP ($r = -0.79$), though the population in their study consisted of individuals with high levels of impairment and disability as indicated by the subjects being primary wheelchair users and bed-ridden.

IMT Training Protocol Comparisons

The pulmonary training protocols used by Gosselink et al,[1] Smeltzer et al,[8] and Klefbeck et al[13] differed somewhat from the training protocol used in this study in both format and intensity (Table 8). A daily training protocol was used in this study and in the studies by Gosselink et al,[1] Smeltzer et al,[8] and Chiara et al,[16] whereas Klefbeck et al[13] asked subjects to train every other day. Training duration extended eight weeks to three months in each study with initial training intensities set at a percent of the MIP or MEP (30% MIP in our study; 40–60% of MIP or MEP,[1,13,16] percent not specified[8]). Exercise intensity was progressed through in-home consultation on a weekly or biweekly basis[8,13,16] or was not specified.[1] The weekly telephone calls to monitor adherence and advance exercise intensity in our study were well received by the subjects and provide a less expensive alternative to weekly or biweekly home visits for exercise progression. The Borg 6–20 RPE scale was used in both our study and Klefbeck et al[13] to monitor subject response to exercise, however use of the Borg 6-20 RPE scale for pulmonary exercise progression in the MS population is unique to this study and provided sufficient guidance for exercise progression.

Limitations of the Study

There are several limitations of the study. To participate in this study subjects had to be ambulatory, placing them in the minimum to moderate disease severity classification according to the EDSS. Therefore, results may not be generalizable to nonambulatory persons with MS. Second, the measures of pulmonary function are largely dependent on the level of the subject's effort and motivation. Third, the multiple trials for each test, although necessary for reproducibil-

TABLE 8. Inspiratory and Expiratory Muscle Training Protocols

Study	EDSS Score	Frequency	Duration	Initial Intensity	Sets and Repetitions	Training Progression Advancement Based On
Inspiratory						
Klefbeck[13]	6.5–9.0	Twice every other day	10 weeks	40–60% MIP	3 sets of 10 repetitions	MIP and RPE , did not specify values
Fry	2.5–6.5	Daily	10 weeks	30% MIP	3 sets of 15 repetitions	Initial MIP, RPE and symptoms per protocol in Table 1
Expiratory						
Smeltzer[8]	6.5–9.5	Twice daily	3 months	Based on MEP, did not specify value	3 sets of 15 repetitions	Tolerance to exercise
Gosselink[1]	7.0–9.5	Twice daily	3 months	60% of MEP	3 sets of 15 repetitions	60% of MEP with threshold adapted for expiratory loading twice daily
Chiara[16]	1.5–6.5	Five days per week	8 weeks	40% of MEP	4 set of 6 reps	40% of MEP progressed to 60% in second week, 80% in third to eighth week

Abbreviations: EDSS, Expanded Disability Status Scale; MIP, maximal inspiratory pressure; RPE, rating of perceived exertion; MEP, maximal expiratory pressure.

ity, may have increased subjects' fatigue levels and decreased performance on remaining measures. This was not found to be a limiting factor in this study based on reported RPE values following each pulmonary test. Fourth is the potential ceiling effect of the IMT device which occurs when a subject reaches a maximal level of resistance (41 cm H_2O) before the end of the intervention period. This ceiling effect occurred with one subject in this study and was addressed by increasing the sets and repetitions when the maximum available resistance was achieved by the subject.

Clinical Implications

Respiratory complications are recognized as the major cause of morbidity and mortality in individuals with advanced MS.[1,2,8–11] Examination of respiratory function should become a routine part of any physical examination of persons with MS. Expiratory muscle training effectively improves expiratory muscle strength in both less disabled and more disabled persons with MS.[1,8,16] IMT effectively improves inspiratory muscle strength in both less disabled (this study) and more disabled persons with MS.[13] Enhanced pulmonary function in persons with MS may increase effectiveness of a cough, improve speech, reduce bouts of pneumonia, improve performance of ADL, increase tolerance for exercise training, and improve quality of life. Future studies are needed that focus on: (1) long-term effects of IMT with increasing resistance; (2) impact of IMT on increasing pulmonary function and functional performance; (3) measuring changes in speech, cough, and number of respiratory infections; and (4) efficacy of IMT compared to expiratory muscle training related to fatigue, pulmonary function, physical performance and function, and quality of life.

CONCLUSION

Of 46 subjects with MS who participated in pretesting, 20 subjects were classified as having obstructive disease and one subject was classified as having restrictive disease indicating a high frequency of pulmonary impairment. IMT was effective in increasing pulmonary function in this population of subjects with mild to moderate disability. Specifically, MIP increased 80.9% following IMT in the I group. There was a clinically important positive effect on expiratory pulmonary function measures such as FVC, FEV_1, FEV_1/FVC, and $FEF_{25–75\%}$ substantiating the indirect positive effects of IMT on expiratory pulmonary function. The inspiratory training overload used in this study resulted in nonspecific or generalized improvements in expiratory pulmonary function.

Pulmonary function should be tested in all persons who have MS, and respiratory muscle training included in therapy programs when pulmonary function is impaired. Persons with MS with mild to moderate disability related to their MS benefit from IMT.

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REFERENCES

1. Gosselink R, Kovacs L, Ketelaer P, et al. Respiratory muscle weakness and respiratory muscle training in severely disabled multiple sclerosis patients. *Arch Phys Med Rehabil*. 2000;81:747–751.
2. Gosselink R, Kovacs L, Decramer M. Respiratory muscle involvement in multiple sclerosis. *Eur Respir J*. 1999;13:449–454.
3. Tantucci C, Massucci M, Piperno R, et al. Control of breathing and respiratory muscle strength in patients with multiple sclerosis. *Chest*. 1994;105:1163–1170.
4. Mutluay FK, Gurses HN, Saip S. Effects of multiple sclerosis on respiratory functions. *Clin Rehabil*. 2005;19:426–432.
5. Howard RS, Wiles CM, Hirsch NP, et al. Respiratory involvement in multiple sclerosis. *Brain*. 1992;115:479–494.
6. Rasova K, Brandejsky P, Havrdova E, et al. Spiroergometric and spirometric parameters in patients with multiple sclerosis: are there any links between these parameters and fatigue, depression, neurological impairment, disability, handicap and quality of life in multiple sclerosis. *Mult Scler*. 2005;11:213–221.
7. Savci S, Inal-Ince D, Arikan H, et al. Six-minute walk distance as a measure of functional capacity in multiple sclerosis. *Disabil Rehabil*. 2005;27:1365–1371.
8. Smeltzer SC, Lavietes MH, Cook SD. Expiratory training in multiple sclerosis. *Arch Phys Med Rehabil*. 1996;77:909–912.
9. Pittock SJ, Mayr WT, McClelland RL, et al. Change in MS-related disability in a population-based cohort: A 10-year follow-up study. *Neurology*. 2004;62:51–59.
10. Renzetti AD, Bleecker ER, Epler GR, et al. Evaluation of impairment and disability due to respiratory disease. *Am Rev Respir Dis*. 1986;133:1205–1209.
11. Redelings MD, McCoy L, Sorvillo F. Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001. *Neuroepidemiology*. 2006;26:102–107.
12. Smeltzer SC, Lavietes MH, Troiano R, et al. Testing of an index of pulmonary dysfunction in multiple sclerosis. *Nurs Res*. 1989;38:370–374.
13. Klefbeck B, Nedjad JH. Effect of inspiratory muscle training in patients with multiple sclerosis. *Arch Phys MedRehabil*. 2003;84:994–999.
14. Buyse B, Demedts M, Meekers J, et al. Respiratory dysfunction in multiple sclerosis: a prospective analysis of 60 patients. *Eur Respir J*. 1997;10:139–145.
15. Smeltzer SC, Skurnick JH, Troiano R, et al. Respiratory function in multiple sclerosis: utility of clinical assessment of respiratory muscle function. *Chest*. 1992;101:479–484.
16. Chiara T, Martin D, Davenport P, et al. Expiratory muscle strength training in persons with multiple sclerosis having mild to moderate disability: effect on maximal expiratory pressure, pulmonary function, and maximal voluntary cough. *Arch Phys Med Rehabil*. 2006;87:468–473.
17. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription.* 7th ed. Baltimore, MD: Williams & Wilkins; 2002; 39–54.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology*. 1983;33:1444–1452.
19. Krupp LB, LaRocca NG, Muir–Nash J, et al. The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46:1121–1123.
20. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med*. 2002;166:518–624.
21. Smeltzer SC, Utell MJ, Rudick RA, et al. Pulmonary function and dysfunction in multiple sclerosis. *Arch Neurol*. 1988;45:1245–1249.
22. American Thoracic Society/European Respiratory Society. Standardisation of lung function testing: standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
23. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis*. 1991;144:1202–1218.
24. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377–381.
25. Grasso MG, Lubich S, Guidi L, et al. Cerebellar deficit and respiratory impairment: a strong association in multiple sclerosis. *Acta Neurol Scand*. 2000;101:98–103.
26. Centers for Disease Control and Prevention. Cigarette smoking attributable morbidity–U.S., 2000. *Morb Mortal Wkly Rep*. 2003;52:843.

