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Clinical trial

Effects of inspiratory muscle training in advanced multiple sclerosis

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ABSTRACT

Background: Respiratory training using Threshold Inspiratory Muscle Trainer (IMT) has not been examined adequately in multiple sclerosis (MS). The primary objective in this study of persons with advanced MS was to investigate the training effect of IMT. The secondary objective was to evaluate the retention of IMT benefits.
Methods: This study was a repeated measures within-subject design (before-after trial).. Participants were recruited from a long-term care facility specialized in progressive neurologic conditions. Thirty-six non-ambulatory persons with advanced MS volunteered. Inspiratory muscle exercise using the threshold IMT were performed daily for 10 weeks at 3 sets of 15 repetitions per day. Resistance was progressed weekly based on perceived rate of exertion and symptoms. Primary outcome measures were maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) that were measured at baseline, after 5 and 10 weeks of IMT exercises (training period), and at 4 and 8 weeks after the IMT training ended (retention). Linear mixed-effect regression models with time (i.e. weeks from baseline) as the fixed factor and participants as the random effect factor were applied separately to test each hypothesis. Effect size was calculated using partial eta square (η2p). Two-tailed significance level was $p < 0.05$.
Results: Participants were 60.5 ± 8.6 years old. Expanded Disability Status Scale was 8.5 ± 0.4. Baseline MIP were 25.9 ± 16.4 cmH2O (33.2% % ± 19.8% of predicted values) and MEP were 23.5 ± 15.7 cmH2O (25.8% % ± 14.4% of predicted values). Compared to the baseline, MIP increased significantly to 30.1 ± 17.9 cmH2O (38.9% % ± 22.4% of predicted values) and 30.6 ± 17.6 cmH2O (39.6% % ± 22.3% of predicted values) after 5 ($p < 0.05$) and 10 weeks ($p < 0.05$) of IMT exercises. MIP improvements were retained in an 8-week washout period. MEP did not differ significantly by time.
Conclusion: In persons with advanced MS, 10-week IMT training increased inspiratory muscle strength. This study is the first to demonstrate the retention of benefits following daily IMT exercises at 8 weeks after training ended.

1. Introduction

Multiple sclerosis (MS) is a chronic debilitating disorder with pathological hallmarks of demyelination, axonal or neuronal loss, and astrocytic gliosis (Reich et al., 2018; Thompson et al., 2018). Clinical features of MS vary widely, depending on the areas of central nervous system affected and the extent of inflammation process and axonal demyelination (Reich et al., 2018). Weakness of respiratory muscles occurs frequently and early in the course of MS, even when pulmonary function is normal or near normal (Fry et al., 2007; Altintas et al., 2007). Among ambulatory persons with MS, more than 60% were found to have impairments in respiratory muscle strength (Fry et al., 2007). Weakness of respiratory muscle is a significant problem in advanced MS. Among hospitalized patients with MS (median Expanded Disability Status Scale (EDSS) score of 6.5), 84% and 98% had impaired inspiratory and expiratory muscle strength, respectively (Buyse et al., 1997). The reduction of respiratory muscle strength correlates with impairments in pulmonary function (Levy et al., 2017; Mutluay et al., 2005), limitations in functional capacity (Bosnak-Guclu et al., 2012), and severity of MS disability (Mutluay et al., 2005; Bosnak-Guclu et al., 2012; Smeltzer et al., 1992; Gosselink et al., 2000). Respiratory muscle weakness ultimately leads to respiratory dysfunction (Tzelepis and

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McCool, 2015), which is the most common cause of critical illness and death in MS (Karamyan et al., 2016; Hirst et al., 2008). Additionally, mortality from respiratory diseases is 5–11 times higher in persons with MS compared to those without MS (Hirst et al., 2008). In light of these severe consequences, interventions to improve respiratory muscle function in MS are imperative.

Respiratory muscle weakness in MS is related to multiple factors, including demyelination of respiratory motor pathways, physical inactivity and deconditioning, and fatigue (Tzelepis and McCool, 2015; Motl and Goldman, 2011). Strengthening respiratory muscles through exercises may enhance respiratory function (Sapienza and Wheeler, 2006) and promote neuroplastic changes (Johnson and Mitchell, 2013). Research evidence of neuroplasticity and specificity and overload principles of exercises suggests that respiratory muscle training needs to be specific to inspiratory or expiratory muscles and delivered at sufficient intensity and loads (Flachenecker, 2015; Smeltzer et al., 1996; Rietberg et al., 2017). Training of respiratory muscles typically utilizes threshold devices that provides resistance during inspiration or expiration, thereby strengthening respiratory muscles (Fry et al., 2007; Smeltzer et al., 1996). Currently there is a lack of clear guidelines for respiratory rehabilitation in MS (Rietberg et al., 2017; Haselkorn et al., 2015). Few studies have reported outcomes of inspiratory muscle exercises in MS. In ambulatory persons with mild-moderate MS (EDSS = 2.0–6.5), a 10-week daily exercise program using a threshold inspiratory trainer (IMT) demonstrated significant gains in inspiratory muscle strength (Fry et al., 2007). Only one study has examined inspiratory muscle training using IMT in advanced MS (EDSS = 6.5–9.0) (Klefbeck and Hamrah Nedjad, 2003). After performing the exercises every other day for 10 weeks, participants significantly improved inspiratory muscle strength, and the benefit was retained one month after the intervention ended (Klefbeck and Hamrah Nedjad, 2003). More research evidence is necessary in order to inform clinical recommendations on effective protocols of respiratory rehabilitation in MS. Respiratory interventions are particularly critical for persons with severe disability from MS who are most susceptible to respiratory dysfunction and complications.

The purposes of this study were to investigate: (1) the training effect of 10-week, daily IMT exercises on respiratory muscle strength, and (2) retention of IMT training benefits over an 8-week non-treatment washout period in non-ambulatory persons with MS. It was hypothesized that participants would (1) improve respiratory muscle strength at the end of IMT program, and (2) retain the gains in respiratory muscle strength at 8 weeks after IMT training ended.

2. Material and methods

2.1. Design

This study is a repeated measures within-subject design.

2.2. Participants

We recruited patients at The Boston Home, a long-term care facility specializing in providing care for individuals with MS and progressive neurologic conditions. Inclusion criteria were age > 18 years, MS diagnosis confirmed from medical records, and EDSS ≥ 6.5. Exclusion criteria were hospitalization for MS exacerbation within two months before or during enrollment, acute illness, unstable cardiovascular or medical conditions, and current smoking history. All participants provided consent prior to enrolling in the study. Information of participants' characteristics was collected via interview and review of medical records at baseline, including demographics, comorbidity measured by Functional Comorbidity Index (Groll et al., 2005), body mass index, EDSS score (Kurtzke, 1983), and years post MS diagnosis. The University of Michigan-Flint Institutional Review Board approved the study.

Table 1
Ten-week home IMT exercise training protocol.*

Frequency: IMT exercises performed daily for 10 weeks.
Overload: Repetition and Set: Three sets of 15 repetitions†
Resistance: Initial resistance (cmH2O) of the IMT was set at 30% of the subjects pretest MIP.
Progression: Subjects were called once per week by one 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.
Resistance: Initial resistance (cmH2O) of the IMT was set at 30% of the participant's baseline MIP.
Profession: Resistance was adjusted weekly according to the participant' baseline MIP, Borg RPE, and symptoms.

Subject's Baseline MIP Pressure < 50 cmH2O				
Borg RPE	< **13**	13 – 15	**16 – 17**	> **17**
Pressure resistance (cmH2O)	Increase by 2	Increase by 1	Maintained at same level	Reduce by 2
Subject's Baseline MIP > 50 cmH2O				
Borg RPE	< **13**	**13 – 15**	**16 – 17**	> **17**
Pressure resistance (cmH2O)	Increase by 4	Increase by 2	Maintained at same level	Reduce 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
IMT Resistance:	Reduce 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 cmH2O 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, maximum inspiratory pressure; RPE, rating of perceived exertion.

* Reproduced with permission from Fry et al., Randomized control trial of effects of a 10-week inspiratory muscle training program on measures of pulmonary function in persons with multiple sclerosis. Journal of Neurologic Physical Therapy, 2007;31(4):162–172. The original protocol shown in the Table was for a home-based program using telephone to monitor and progress the exercises. Participants in this study, however, were contacted in person by research personnel.

2.3. Sample size

G* Power (Faul et al., 2007) was used to estimate the sample size, with alpha level = 0.05, power = 0.80, and effect size = 0.69 (Cohen's d based on published data (Fry et al., 2007)). For a study design of within-subject comparison, a minimum of 34 participants would be required, and 37 participants were recruited to increase the power and account for attrition.

2.4. Intervention

Each participant was given a Threshold Inspiratory Muscle Trainer (IMT) (Philips, Andover, MA)[a] for the 10-week inspiratory exercise program. The progression of IMT exercises followed a published protocol in mild-moderate MS (Table 1) (Fry et al., 2007).

The original protocol was a home-based program using telephone to communicate with participants (Fry et al., 2007). In this study, however, participants were contacted in person to monitor and progress their exercises. Participants performed 3 sets of 15 repetitions of IMT exercises daily for 10 weeks from a seated position (Fig. 1).

An exercise log was provided to each participant to document the number of repetitions completed every day. Research personnel gave exercise instructions to participants prior to starting the training, and rehabilitation aides provided supervision and assistance as necessary during exercises. The initial IMT resistance was set at 30% of participant's baseline MIP values, or at the minimum setting (9 cmH2O) when

Fig. 1. Participant positioning for inspiratory muscle exercises.
Participant performed the exercises using a hand-held inspiratory muscle trainer from a seated position.

the participant's 30% of baseline MIP was below the lowest resistance possible on the IMT device. The resistance of IMT was adjusted weekly based on each participant's baseline MIP, symptoms (e.g. discomfort, shortness of breath, dizziness, or lightheadedness) reported during the week, and tolerance of the exercise evaluated by Borg Rate of Perceived Exertion (RPE) on the last day of the week (Borg, 1982).

2.5. Primary outcomes

Inspiratory and expiratory muscle strength was evaluated by maximal inspiratory pressure (MIP) and maximum expiratory pressures (MEP), respectively (Fig. 2) (ATS/ERS Statement on respiratory muscle testing, 2002).

A MicroRPM Pressure Meter (Micro Direct, Inc. Lewiston, ME)[b] was used to measure MIP and MEP five times in the study: prior to the start of IMT training (baseline), after 5 (post-test 1) and 10 weeks (post-test 2) of IMT training, and at 4 (retention test 1) and 8 weeks (retention test 2) after completing IMT training. All testers completed training of the standardized measurement protocol of MicroRPM (ATS/ERS Statement on respiratory muscle testing, 2002). To measure MIP and MEP, participants placed the device (with a flanged mouthpiece) within mouth, wore a nose clip to prevent air leak, and then inhaled or exhaled as much as possible and sustained a maximal inspiration or expiration for at least 1.5 s (ATS/ERS Statement on respiratory muscle testing, 2002). Three trials of MIP and 3 trials of MEP were obtained. The best values from the 3 trials were used for statistical analysis. MIP and MEP values were also expressed as percentages of age- and gender-adjusted predicted values (Evans and Whitelaw, 2009).

Fig. 2. Participant positioning and equipment for maximum inspiratory and expiratory pressure testing.
Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were measured from a seated position. A MicroRPM Pressure Meter (Micro Direct, Inc. Lewiston, ME) with a flanged mouthpiece was used. Participants wore a nose clip to prevent air leak and then inhaled or exhaled as much as possible through the device. Three trials of MIP and 3 trials of MEP were obtained. The best values from the 3 trials were analyzed.

2.6. Statistical analysis

IBM-SPSS version 24 (Armonk, NY) was used for statistical analysis. Descriptive statistics were calculated for participant characteristics and primary outcomes. The independent variable was time, i.e. weeks from baseline. A linear mixed-effects regression model was applied separately to test each hypothesis, with time as a fixed effect factor and participants as a random effect factor. To test hypothesis 1 for the IMT training effects, dependent variables for the model were MIP and MEP at baseline, post-test 1, and post-test 2. To test hypothesis 2 for the retention of IMT training benefits, dependent variables for the model were MIP and MEP at post-test 2, retention test 1, and retention test 2. Post-hoc comparisons were adjusted by the Bonferroni correction. Effect size was calculated using partial eta square ($\eta 2p$). Criteria for evaluating the effect size were 0.01 = small, 0.06 = medium, and 0.14 = large (Fritz et al., 2012). Two-tailed significance level was $p < 0.05$.

3. Results

3.1. Participant characteristics

A total of 37 patients participated. One dropped out due to declining health and prolonged illness. One participant did not complete retention tests as a result of acute hospitalization from non-respiratory related conditions. Data from 9 men and 27 women were retained for analysis. All participants were breathing room air without supplementary oxygen or mechanical ventilation, and were able to cooperate to complete measurements during the study period. The participants were 60.5 ± 8.6 years old and 27.6 ± 10.4 years post-MS diagnosis. Functional comorbidity index was 2.3 ± 2.0. Body mass index was 26.5 ± 6.1. Disability related to MS was severe as evidenced by the EDSS score of 8.5 ± 0.4 (range 8.0–9.5). At baseline, MIP and MEP were well below age- and gender-adjusted predicted values (Table 2). Specifically 92% (n = 33) and 97% (n = 35) of participants had MIP and MEP below 60% of predicted values, respectively, indicating impaired inspiratory and expiratory muscle strength (Evans and Whitelaw, 2009).

3.2. Progression of IMT exercises

The initial IMT resistance was set at 30% of each individual's baseline MIP, or at the lowest resistance setting of 9 cmH2O if the individual's 30% baseline MIP was less than 9 cmH2O. Ten subjects initiated IMT exercises at 30% of baseline and the remaining 26 subjects initiated IMT exercises at 9 cmH2O. Two participants had baseline MIP values above 50 cmH2O and increased weekly IMT resistance at greater increments than other participants per the study protocol. Overall, participants increased the IMT resistance from 10.3 ± 3.1 cmH2O during week 1–25.4 ± 4.2 cmH2O during week 10 (Fig. 3).

Only one participant achieved the maximum IMT resistance of 41 cmH2O and added a fourth set of exercise at the end of week 5. Borg RPE was 9.1 ± 2.5 (range 6–15) at the end of week 1 and increased to

Table 2
Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) at baseline, after 5 weeks and 10 weeks of Threshold Inspiratory Muscle Trainer (IMT) exercises.

Variable	Baseline	5 Weeks of IMT	10 Weeks of IMT	*p*-value
MIP (cmH2O)	25.9 ± 16.4	30.1 ± 17.9[a]	30.6 ± 17.6[a]	0.013
MIP (% of predicted value)	33.2 ± 19.8	38.9 ± 22.4[a]	39.6 ± 22.3[a]	0.011
MEP (cmH2O)	23.5 ± 15.7	25.0 ± 13.7	24.4 ± 12.9	0.639
MEP (% of predicted value)	25.8 ± 14.4	27.8 ± 15.0	27.4 ± 13.4	0.330

Values are expressed as mean ± SD.
p-values are for the effect of time for the variable.
[a] $p < 0.05$ for post-hoc pairwise comparisons of MIP after 5 weeks and 10 weeks of IMT in comparison with baseline after adjustment using Bonferroni correction.

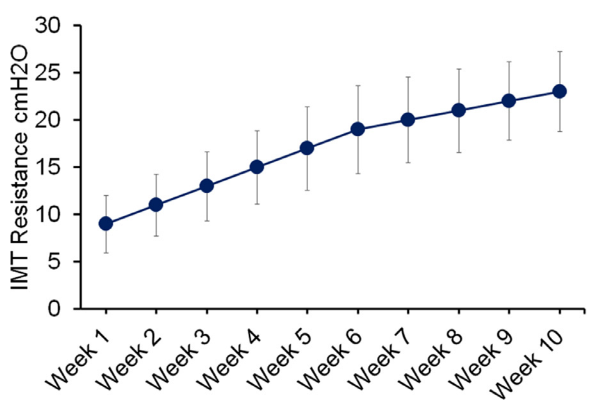

Fig. 3. Progression of IMT resistance during training.
The average resistance of inspiratory muscle trainer (IMT) for participants from week 1 to week 10 is shown. The initial IMT resistance was set at 30% of each individual's baseline maximum inspiratory pressure (MIP), or at the lowest resistance setting of 9 cmH2O if the individual's 30% baseline MIP was less than 9 cmH2O. At the end of each week, the IMT resistance was adjusted based on the Borg rate of perceived exertion (RPE) on the last day of the week and symptoms reported during the week, such as discomfort, shortness of breath, dizziness, or lightheadedness. The weekly IMT resistance was increased or decreased by 1 to 4 cmH2O, or remained unchanged depending on each participant's RPE and symptoms. Refer to the Methods section for detailed descriptions about the progression of weekly IMT resistance.

11.2 ± 2.6 (range 6–15) at the end of week 9 (Fig. 4).

The highest Borg RPE was 17 reported by two participants (once per participant). Participants tolerated the inspiratory exercises well without adverse events. The exercise logs documented that participants completed 47% % ± 29% of prescribed repetitions during the 10-week IMT training.

3.3. Training effect of IMT exercises

As shown in Table 2, MIP actual and predicted values increased after IMT exercises. After 10 weeks of IMT, MIP increased by 4.7 ± 10.9 cmH2O and 6.4 ± 13.9% of predicted value from baseline. These improvements were approximately 18% and 19% of participants' baseline MIP actual and predicted values, respectively. Results of linear mixed-effects model showed that MIP differed significantly by time ($p = 0.013$ for MIP actual values; $p = 0.011$ for MIP predicted values). Post-hoc tests with Bonferroni corrections revealed that in comparison with baseline, MIP was significantly higher after 5 weeks of IMT exercises ($p = 0.046$, $\eta 2p = 0.16$ for MIP actual values; $p = 0.042$, $\eta 2p = 0.18$ for MIP predicted values) and after 10 weeks of IMT

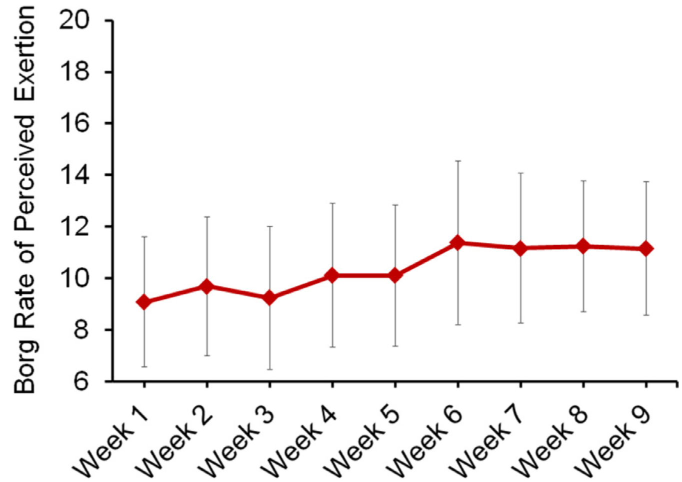

Fig. 4. Changes in Borg rate of perceived exertion during training.
The average weekly Borg rate of perceived exertion (RPE) of participants during the 10 weeks of inspiratory exercises is shown. Participants rated RPE on the last day of each week. The average weekly RPE values for participants during training were between 9 and 12.

exercises ($p = 0.022$, $\eta 2p = 0.16$ for MIP actual values; $p = 0.019$, $\eta 2p = 0.18$ for MIP predicted values). The effect sizes for gains in MIP after 5 weeks and 10 weeks of IMT were large. Table 2 also presents MEP actual and predicted values at baseline, after 5 weeks and 10 weeks of IMT exercises. Linear mixed-effects model analysis indicated that MEP did not differ significantly by time.

3.4. Retention of IMT training benefits

Table 3 presents MIP and MEP actual and predicted values at the end of 10-week IMT exercises, and at 4 weeks and 8 weeks after completing IMT. Results of linear mixed-effects model showed that MIP and MEP did not differ significantly by time. The improvements in MIP attained at the end of 10-week IMT exercises were retained at 4 weeks and 8 weeks after IMT training ended.

4. Discussion

In advanced MS, daily inspiratory muscle exercises using threshold loading with progressive resistance for 10 weeks significantly improved MIP but not MEP, suggesting a task-specific training effect of IMT on inspiratory muscles. This study was the first to demonstrate the retention of improvements in MIP at 8 weeks post IMT training in non-ambulatory persons with advanced MS. More importantly, participants reported no adverse events, supporting the feasibility of IMT training at 3 sets of 15 repetitions every day for 10 weeks.

Table 3
Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) immediately after 10 weeks of Threshold Inspiratory Muscle Trainer (IMT) exercises, and at 4 weeks and 8 weeks after IMT ended.

Variable	Post-IMT	4 Weeks Post-IMT	8 Weeks Post-IMT	*p*-value
MIP (cmH2O)	31.0 ± 17.6	29.4 ± 18.2	29.2 ± 18.7	0.314
MIP (% of predicted value)	40.1 ± 22.4	38.3 ± 23.9	37.7 ± 23.9	0.308
MEP (cmH2O)	24.6 ± 12.9	24.5 ± 12.6	24.5 ± 14.3	0.982
MEP (% of predicted value)	27.5 ± 13.5	27.1 ± 12.8	26.7 ± 14.3	0.827

Values are expressed as mean ± SD.
p-values are for the effect of time for the variable.

Previous research has documented impaired respiratory muscles in MS and expiratory muscles were more affected than inspiratory muscles. (Levy et al., 2017; Smeltzer et al., 1992; Gosselink et al., 2000) Consistent with past research, this study also found that in advanced MS, respiratory muscle strength was severely limited as evidenced by low MIP and MEP at baseline. Nearly all of the participants had inspiratory and expiratory muscle weakness, as indicated by MIP ad MEP below 60% of predicted values (Evans and Whitelaw, 2009). Levy et al. (2017) reported that among non-ambulatory (EDSS = 7.5–8.5), medically stable, hospitalized MS patients without MS relapses, pneumonias, or other infections, MIP and MEP were 33.1 ± 23.7% and 26.9% ± 22.1% of predicted values, respectively. Similarly, Gosselink et al. (2000) reported low MIP (27% ± 11%) and MEP (18% ± 8%) in MS patients with EDSS ranging from 6.5 to 9.5. These findings taken together with ours suggest that, impairments in both inspiratory and expiratory respiratory muscle strength are severe and highly prevalent in advanced MS, highlighting the need to investigate interventions to improve respiratory muscle function.

To date only two studies had examined the effects of inspiratory exercises using threshold loading in MS (Fry et al., 2007; Klefbeck and Hamrah Nedjad, 2003). Following the IMT training, positive outcomes on MIP were observed consistently across studies (Fry et al., 2007; Klefbeck and Hamrah Nedjad, 2003) and improvements in MEP were reported in one study (Klefbeck and Hamrah Nedjad, 2003). The IMT training protocol used in this study had previously demonstrated efficacy in increasing MIP by 23.5 cmH2O and 40.6% of predicted values in mild-moderate MS (EDSS ≤ 6.5) (Fry et al., 2007). Klefbeck and Hamrah Nedjad (2003) reported that in advanced MS (EDSS = 6.5–9.0), a 10-week IMT exercises performed twice every other day, at 3 sets of 10 repetitions per session, significantly improved MIP by 25 cmH2O and MEP by 17 cmH2O. In this study, the IMT training did not impact MEP, but increased MIP significantly by nearly 20% of baseline MIP values with large effect sizes. Minimal clinically important differences for MIP and MEP in MS have not yet been established, therefore precluding the interpretation of current findings in the context of clinically meaningful changes. The retention of improvements in MIP had been reported in MS at 4 weeks after IMT training ended (Klefbeck and Hamrah Nedjad, 2003). During the 8-week retention period, our participants retained gains in MIP attained after training, supporting the benefits of IMT exercises.

IMT training parameters and participant characteristics, such as practice setting, age, impairments and disability from MS varied among current and previous studies (Fry et al., 2007; Klefbeck and Hamrah Nedjad, 2003). The numbers of IMT training sessions ($n = 70$) and exercise repetitions per session ($n = 30$) were equivalent across IMT protocols being reported (Fry et al., 2007; Klefbeck and Hamrah Nedjad, 2003). Our participants on average completed about 47% of exercise repetitions prescribed during the 10-week IMT training, which was approximately half of the exercise dosage reported in previous protocols (Fry et al., 2007; Klefbeck and Hamrah Nedjad, 2003). It cannot be ruled out that some participants had not recorded the exercise repetitions being completed in the daily log. The initial IMT resistance was higher in the study by Klefbeck et al. (40%–60% of pre-training MIP) (Klefbeck and Hamrah Nedjad, 2003) in comparison with this study (30% of pre-training MIP or 9 cmH2O). Additionally, we recruited individuals who were functionally dependent with advanced MS and required specialized residential care at a long-term care facility. Participants in previous studies were recruited from the community (Fry et al., 2007) or outpatient clinics (Klefbeck and Hamrah Nedjad, 2003), and were likely functioning at a higher level with less disability. Indeed, participants with advanced MS in the previous study had higher pre-training MIP predicted values (59% ± 25%) (Klefbeck and Hamrah Nedjad, 2003) compared to our participants (33.2% ± 19.8%). Whether exercise dosage, pre-training MIP and MEP levels, or other clinical features influence IMT training outcomes remains to be examined. A recent study indicated that responses to exercise training were highly heterogenic in persons with MS (Baird and Motl, 2018). Genetics, pre-training functional level, parameters of training protocols, MS disease-specific characteristics and symptom burden, and damage to the nervous system are possible factors influencing individual responses to exercises (Baird and Motl, 2018).

Current findings support that similar to skeletal muscles, respiratory muscles can adapt to resistance exercises and improve strength in advanced MS. Respiratory muscle training outcomes may depend on the task performed during exercises. The IMT training specifically enhanced inspiratory muscle strength, which was targeted during inspiratory exercises. Muscular and neural mechanisms likely have contributed to IMT training outcomes. Progressive resistance training is known to increase muscle strength, muscle fiber cross sectional area, and efferent output of spinal motor neurons in persons with MS (Wens et al., 2015; Kjølhede et al., 2012). Furthermore, existing evidence suggests that active and task-related motor rehabilitation may enhance function and structure of the brain in persons with MS (Prosperini et al., 2015). Studies showed that in mild-moderate MS, high-intensity and task-specific motor training led to changes in activities and structures of white matter tracts as evaluated using advanced neuroimaging techniques (Bonzano et al., 2014; Prosperini et al., 2014). These brain changes correlated with improvements in clinical outcomes, such as bimanual coordination (Bonzano et al., 2014) and standing balance (Prosperini et al., 2014). Similarly, it may be plausible that IMT training led to task-related neuroplastic changes. Future research is warranted to examine the link between improvements in respiratory function and changes in the structure and activities of the central nervous system.

One limitation of this study is the lack of a control group. However, we had a larger sample size than the only other study of advanced MS that compared 7 subjects in the IMT training group with 8 subjects in the control group (Klefbeck and Hamrah Nedjad, 2003). Our sample size was adequate based on a priori power analysis. Repeated measure design chosen for this study is suitable for a chronic stable condition, particularly when randomization may not be acceptable or feasible for participants (Hulley et al., 2013). Generalization of current findings may be limited to non-ambulatory individuals with advanced MS living in long-term care facilities.

More research is necessary to investigate the impact of IMT training on other clinical outcomes, such as fatigue, cognition, respiratory infection, activity and participation. Data analyses to elucidate these relationships are ongoing. Future studies also need to evaluate the outcomes of different IMT protocols, specifically the resistance, frequency, duration, and progression criteria, in order to establish the appropriate training dosage in persons with advanced MS. Factors that potentially impact the responses to respiratory training in persons with MS need to be investigated to inform the design of individualized exercise programs.

5. Conclusions

Non-ambulatory persons with advanced MS in this study showed a positive, task-specific change in inspiratory muscle strength after 5 and 10 weeks of exercises using a low-cost, threshold loading inspiratory training device. These improvements were still evident at 8 weeks after the training ended. Current findings filled the knowledge gap in respiratory muscle training and have important clinical implications by demonstrating the benefits and feasibility of inspiratory exercises with progressive resistance in advanced MS. The optimal IMT training parameters and its impact on clinical outcomes, other than inspiratory muscle strength, is not known and warrants future research.

Declaration of Competing Interest

The authors declared no conflict of interest.

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