Predictors of Improvement in Respiratory Function Following Resistive Inspiratory Muscle Training in Advanced Multiple Sclerosis (REH02)

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INTRODUCTION/OBJECTIVES

Respiratory compromise in people with advanced multiple sclerosis (PwAMS, EDSS≥6.5) worsens as the disease progresses and is a major cause of morbidity and mortality. There is evidence that exercise can improve respiratory muscle function in PwAMS even in the later stages of the disease (Klefbeck et al, 2003; Rietberg et al, 2017). It is not known if certain characteristics of PwAMS contribute to their ability to benefit from a respiratory exercise program. This study aims to identify some possible predictive factors in this population.

STUDY DESIGN & METHODS

•Prospective cohort study (repeated measures within-subject design)

•N = 38 persons recruited from The Boston Home (TBH), a specialized residential and outpatient program for PwAMS and related advanced neurological disorders (see demographics in profile table below)

•Inclusion criteria: age >18 years, MS diagnosis, EDSS≥6.5, non-current smoker, no hospitalization for MS within 2 months prior, no acute illness, and providing consent to participate.

•Participants performed 3 sets of 15 repetitions of resistive inspiratory exercises daily for 10 weeks using the Threshold Inspiratory Muscle Trainer (IMT) (Philips, Andover, MA) using protocol adapted from previous study in persons with mild-moderate MS (Fry et al, 2007). Initial IMT resistance set at 30% of each participant's baseline maximum inspiratory pressure (MIP), or at 9 cmH2O if 30% baseline MIP < 9 cmH2O.

•Progression of IMT resistance adjusted weekly based on symptoms (e.g. shortness of breath, light-headedness, dizziness, or discomfort), rate of perceived exertion, and baseline MIP.

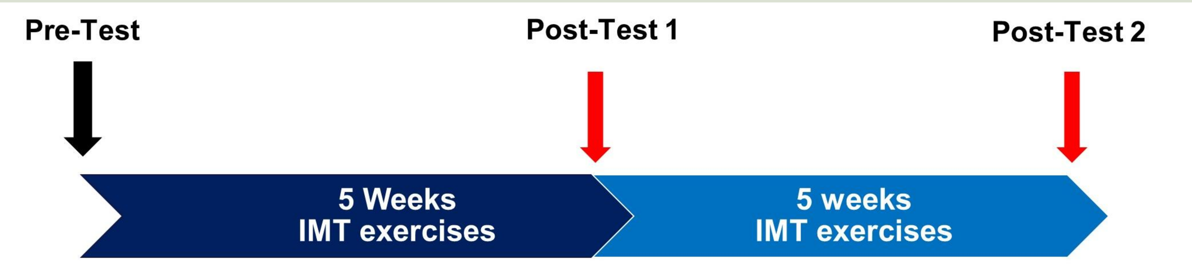
•Participants unable to hold IMT device d/t BUE ataxia or weakness received assistance to complete exercises.

•Additional assessments conducted periodically across study include measures of fatigue (MFIS-5), cognitive processing speed (SDMT), and social participation/QOL (# weekly group activity participation).

Variable	Mean ± SD or Number
Number of Participants	38
% of Trials Completed	45.9% ± 28.6%
Age, year	60.2 ± 8.5
Female	29
Comorbidity	2.3 ± 2.0
Body Mass Index, kg/m^2	26.8 ± 6.1
Years Post Multiple Sclerosis Diagnosis	28.3 ± 11.0
Expanded Disability Status Scale Score	8.5 ± 0.4
Modified Fatigue Impact Scale-5	6.6 ± 4.7
Symbol Digit Modality Test	18.4 ± 10.3
Activity per Week	3.8 ± 2.1
Maximum Inspiratory Pressure, cmH2O	27.9 ± 16.7
Adjusted Maximum Inspiratory Pressure, % of Predicted Value	36.1% ± 21.3%
Maximum Expiratory Pressure, cmH2O	23.7 ± 15.3
Adjusted Maximum Expiratory Pressure, % of Predicted Value	26.1% ± 14.1%

Respiratory muscle strength measurements at pre-test, post-tests 1 and 2

- Maximum inspiratory pressure (MIP)
- Age- and gender-adjusted MIP (MIPp)
- Maximum expiratory pressure (MEP)
- Age- and gender-adjusted MEP (MEPp)



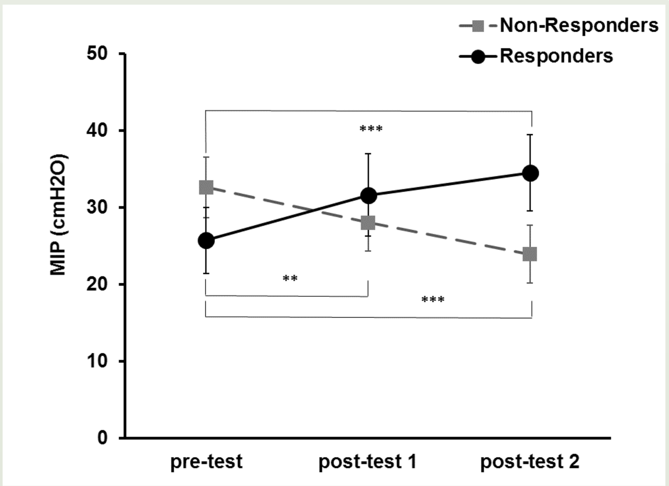
OUTCOMES

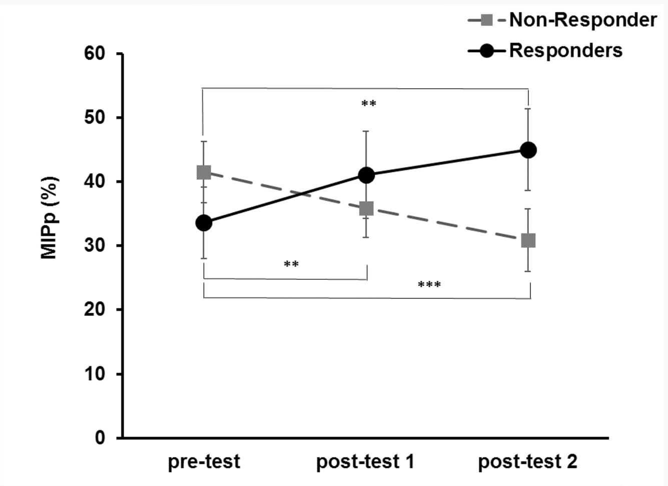
Primary outcomes

- Changes of MIP and MIPp from pre-test to post-test 2. Participants with (+) ΔMIP across these data points were considered "responders;" those without ΔMIP or regressive MIP scores labeled "non-responders" with respect to IMT intervention

Statistical analysis

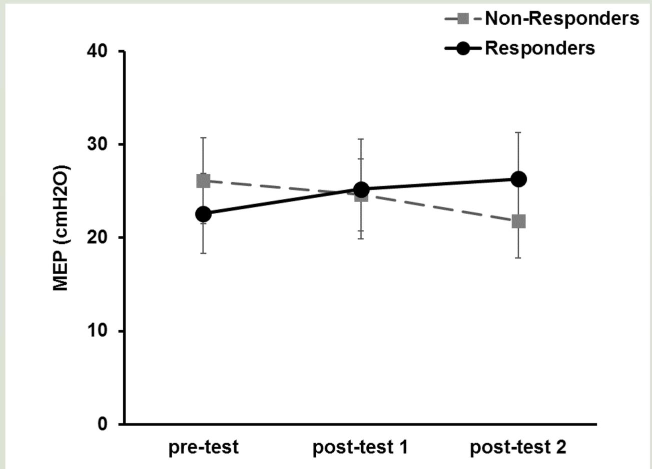
- Descriptive statistics
- Repeated measures mixed design to compare respiratory muscle strength from pre-test to post-test 2 between responders and non-responders to the IMT
- Correlations and backward regression analyses between baseline measurements and primary outcomes
- Two tailed significance level p <0.05

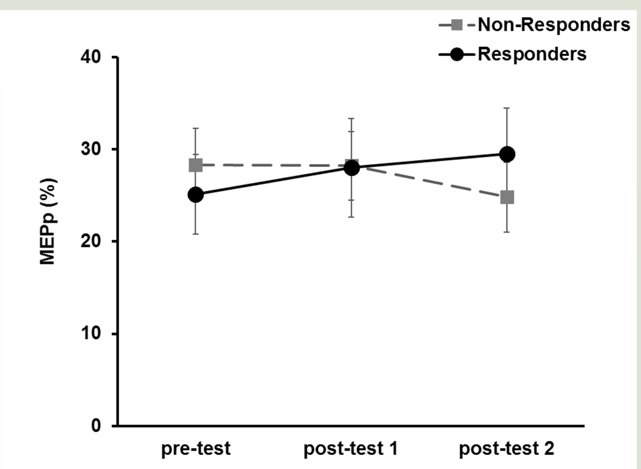




- Time by group interaction was significant for MIP (p < 0.001) and MIPp (p < 0.001).
- Responders improved MIP and MIPp from pre-test to post-test 1 (p = 0.002 for MIP; p = 0.003 for MIPp) and post-test 2 (p < 0.001 for MIP; p < 0.001 for MIPp).
- Non-responders reduced MIP (p < 0.001) and MIPp (p = 0.001) from pre-test to post-test 2.

(** p < 0.01; *** p < 0.001)





- Main effects of time and group were not significant for MEP or MEPp., although similar trend demonstrated slight improvements in these measures for responders vs non-responders (still categorized with respect to MIP outcomes).
- Time by group interaction approached significance level (p = 0.053).
- Post-hoc analysis with Bonferroni adjustment did not reveal any significant differences across time points in either non-responders or responders.

ANALYSIS

Variable	Δ MIP	Δ MIPp	Trial %	Age	Gen	FCI	Year MS	BMI	EDSS	MIP	MIPp	MEP	MEPp	MFIS5	SDMT	Act
Δ MIP	1	0.986, <0.001	0.157, 0.352	-0.008, 0.963	0.063, 0.707	-0.029, 0.862	-0.072, 0.673	-0.332, 0.042	-0.125, 0.474	-0.140, 0.401	-0.201, 0.225	-0.042, 0.801	0.030, 0.858	-0.277, 0.092	0.179, 0.283	0.090, 0.591
Δ MIPp		1	0.203, 0.228	0.039, 0.816	0.110, 0.511	-0.041, 0.807	-0.055, 0.747	-0.343, 0.035	-0.105, 0.548	-0.120, 0.472	-0.194, 0.243	-0.054, 0.746	0.060, 0.721	-0.328, 0.045	0.175, 0.293	0.075, 0.653

Correlation analysis of baseline characteristics with MIP change scores (Δ MIP & Δ MIPp) performed to identify potential predictors of improvements in MIP for the regression analysis.

- Values are expressed as correlation coefficients, p-values.
- Key: Act, activity participation per week; BMI, Body Mass Index; EDSS, Expanded Disability Status Scale; FCI, Functional Comorbidity Index; Gen, gender; MFIS5, Modified Fatigue Impact Scale-5; MIP, maximum inspiratory pressure; MIPp, age- and gender-adjusted maximum inspiratory pressure predicted values; MEP, maximum expiratory pressure; MEPp, age- and gender-adjusted maximum expiratory pressure predicted values; SDMT, symbol digit modality test; Trials%, percentage of completed exercise trials recorded on the daily log; Year MS, years since multiple sclerosis diagnosis.

Primary Outcome: Change in Maximum Inspiratory Pressure from Pre-Test to Post-Test 2

Independent Variable	Coefficient	P value	Model Summary
Body Mass Index	-0.705	0.011	$R^2 = 0.38$ Adjusted $R^2 = 0.31$ $F(4,33) = 5.05$ $p = 0.003$ Constant = 30.18
Modified Fatigue Impact Scale – 5 Items	-1.059	0.005	
Oral Version of Symbol Digit Modality Test	0.431	0.014	
Adjusted Maximum Inspiratory Pressure	-0.229	0.1	

Primary Outcome: Change in Adjusted Maximum Inspiratory Pressure from Pre-Test to Post-Test 2

Independent Variable	Coefficient	P value	Model Summary
Body Mass Index	-0.01	0.004	$R^2 = 0.44$ Adjusted $R^2 = 0.37$ $F(4,33) = 6.34$ $p = 0.001$ Constant = 42.29
Modified Fatigue Impact Scale – 5 Items	-0.015	0.001	
Oral Version of Symbol Digit Modality Test	0.005	0.011	
Adjusted Maximum Inspiratory Pressure	-0.291	0.007	

Multivariable prediction models for Δ MIP & Δ MIPp after a 10-week IMT include the body mass index, scores of Modified Fatigue Impact Scale-5 Items, oral version of Symbol Digit Modality Test, and MIP at baseline.

- All predictors in the models were significantly and independently associated with Δ MIP & Δ MIPp from pre-test to post-test 2.


Wu et al. Int J Chron Obstruct Pulmon Dis. 2017;12:773-781

CONCLUSIONS/FUTURE DIRECTIONS

Participant scores in BMI, MFIS-5, SDMT, and MIPp at baseline significantly predicted Δ MIP and Δ MIPp in this study and analysis. Possible reasons for these correlations include:

•BMI: lower BMI could provide reduced physiological stress during respiratory exercise

•Fatigue: lower fatigue could result in more consistent quantity and duration of prescribed respiratory exercise

•SDMT: higher cognitive processing speed could indicate better likelihood of understanding and following instructions to perform respiratory exercise

•Baseline MIPp: lower adjusted MIP at baseline could result in more room for quantitative improvement, or higher adjusted MIP might require higher threshold of IMT resistance to achieve significant Δ MIPp through respiratory exercise

Factors such as age, gender, duration of disease, EDSS score, and number of comorbidities were not significant predictors of Δ MIP. Nevertheless, the identification of several factors that might be predictive of positive intended response to IMT can help guide clinical decision making as to whether to introduce this respiratory exercise option for PwAMS.

Future studies can compare these outcomes with participants with increased frequency of IMT exercise performance, Δ MEP & Δ MEPp results with the transition to targeted EMST interventions, and implementation of minimal threshold of cognitive processing performance as criteria for inclusion in study protocol. Response heterogeneity to resistive inspiratory exercises likely exists in persons with advanced MS which warrants further research.

KEY REFERENCES

Fry DK, Pfalzer LA, Chokshi AR, Wagner MT and Jackson ES. Randomized control trial of effects of a 10-week inspiratory muscle training program on measures of pulmonary function in persons with multiple sclerosis. J Neurol Phys Ther. 2007; 31(4):162-72.

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Rietberg MB, Veerbeek JM, Gosselink R, Kwakkel G, van Wegen EE. Respiratory muscle training for multiple sclerosis. Cochrane Database Syst Rev. 2017;12:Cd009424.

Related data on primary outcomes from this study can be found here:
Huang MH, Fry D, Doyle L, Burnham A, Houston N, Shea K, Smith H, Wiske L, Goode J, Khitrikc , Kolandac M. Effects of inspiratory muscle training in advanced multiple sclerosis. MS & Related Disorders. 2020;37: 101492.

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