ARTICLE IN PRESS
JID: NMD [m5+;October 27, 2020;8:41]

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ScienceDirect

Neuromuscular Disorders xxx (xxxx) xxx

www.elsevier.com/locate/nmd

Respiratory muscle training in late-onset Pompe disease: Results of a sham-controlled clinical trial

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Received 21 May 2020; received in revised form 12 August 2020; accepted 8 September 2020
Available online xxx

Abstract

To address progressive respiratory muscle weakness in late-onset Pompe disease (LOPD), we developed a 12-week respiratory muscle training (RMT) program. In this exploratory, double-blind, randomized control trial, 22 adults with LOPD were randomized to RMT or sham-RMT. The primary outcome was maximum inspiratory pressure (MIP). Secondary and exploratory outcomes included maximum expiratory pressure (MEP), peak cough flow, diaphragm ultrasound, polysomnography, patient-reported outcomes, and measures of gross motor function. MIP increased 7.6 cmH_2O (15.9) in the treatment group and 2.7 cmH_2O (7.6) in the control group ($P = 0.4670$). MEP increased 14.0 cmH_2O (25.9) in the treatment group and 0.0 cmH_2O (12.0) in the control group ($P = 0.1854$). The only statistically significant differences in secondary/exploratory outcomes were improvements in time to climb 4 steps ($P = 0.0346$) and daytime sleepiness ($P = 0.0160$). The magnitude of changes in MIP and MEP in the treatment group were consistent with our pilot findings but did not achieve statistical significance in comparison to controls. Explanations for this include inadequate power and baseline differences in subject characteristics between groups. Additionally, control group subjects appeared to exhibit an active response to sham-RMT and therefore sham-RMT may not be an optimal control condition for RMT in LOPD.

Keywords: Pompe disease; Late-onset Pompe disease; Respiratory muscle training; Randomized control trial; Maximum inspiratory pressure; Maximum expiratory pressure.

1. Introduction

Pompe disease is an autosomal recessive inherited progressive metabolic myopathy that results in skeletal, cardiac, and smooth muscle weakness, respiratory muscle involvement, and early death. Deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA) causes tissue destruction and muscle fiber atrophy [1]. Pompe disease manifests clinically across a spectrum based on age of onset, progression rate, genetic mutation(s), and disease distribution [2]. Late-onset Pompe disease (LOPD) presents as a spectrum of disease involvement from the first year of life to patients who present in adulthood with signs and symptoms related to progressive weakness in the lower limbs, trunk, and respiratory muscles [3–5]. Despite enzyme replacement therapy (ERT) with alglucosidase alfa, (Lumizyme®), respiratory muscle weakness often persists

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https://doi.org/10.1016/j.nmd.2020.09.023
0960-8966/

and remains a primary cause of morbidity and mortality in LOPD. Respiratory weakness in LOPD leads to ineffective cough and reduced airway clearance [6], sleep-disordered breathing [7], and progressive respiratory insufficiency.

Over 18 months of treatment with ERT in LOPD, walking distance is improved and pulmonary function is stabilized based on forced vital capacity. Modest increases in respiratory strength are achieved 12 to 26 weeks after initiation of ERT in roughly two-thirds of patients [3,8]. Thus, up to a third of patients exhibit no improvements, and, in those who do, these effects on respiratory strength either remain stable or diminish over time. Recent data from 177 LOPD patients were unable to detect the effect of ERT on the subsequent need for respiratory support [9]. While treatments such as bi-level ventilation and cough-assisting devices may improve survival, they do not modulate progressive respiratory weakness. Advanced disease progression at the time of initiation of ERT may limit the reversal of motor and pulmonary signs associated with disease phenotype [10,11]. Therefore, despite drug therapy, respiratory muscle weakness remains an unmet medical need in LOPD. Though next generation therapies currently under development appear to hold promise [12], adjunctive treatments to prevent ongoing progression of disease severity may still provide meaningful improvements in patients' quality of life. Counteracting respiratory weakness with resistance training offers a plausible biological mechanism to address this clinical gap. In response, we have developed a 12-week RMT program that provides calibrated, individualized, progressive pressure-threshold resistance against inspiration and expiration [13-16].

Although patients with muscle disease were once discouraged from exercise, consensus guidelines now support supervised exercise programs in patients with Pompe disease [4,17]. Whole body exercise studies involving resistance and/or aerobic training in humans with LOPD on ERT suggest that supervised exercise programs are safe and well-tolerated, benefit muscular strength and functional capacity, and improve pain and fatigue [18–22]. Therefore, supervised programs of submaximal exercise training are increasingly thought to have value as both adjunctive treatments to ERT and as part of the comprehensive treatment of LOPD.

There has also been increased interest, including our own, in the use of RMT to provide resistance training to the inspiratory and/or expiratory muscles directly in patients with LOPD on ERT [13–16,23–25]. Overall, these studies, albeit in relatively small groups of subjects, suggest that RMT in LOPD is safe and well-tolerated and may be a useful intervention to increase respiratory muscle strength.

Although preliminary data from our laboratory and others are promising, RMT research with a control group has not previously been conducted in LOPD. Therefore, we investigated the effects of our 12-week RMT regimen in a group of 22 adults with LOPD in an exploratory, double-blind, randomized control trial (RCT) using a parallel arm pretest-posttest design and sham-RMT as the control condition. Our aims were to: 1) determine the utility and feasibility of sham-RMT as a control condition for RMT in a double-blind RCT, and 2) determine the clinically meaningful outcomes for inclusion in future clinical trial.

2. Methods

Comprehensive, detailed information regarding the design of our trial and the methodology employed was previously published and the reader is referred to this manuscript for a full description of our methods [15]. A brief review is provided below. This study was registered in a publicly accessible clinical trials database (clinicaltrials.gov identifier: NCT02801539). The Duke University Health System Institutional Review Board approved this research and informed consent was obtained from each participant.

2.1. Participants

Inclusion criteria included age $\geq$ 18 years, diagnosis of LOPD, on enzyme replacement therapy for $\geq$ 26 weeks at pretest, able to follow directions for study participation, and able to complete a home-based RMT regimen. Exclusion criteria included neurodegenerative conditions (e.g. stroke, dementia) or other serious neurologic condition that would prevent meaningful study participation as determined at the discretion of the PI, inability to give legally effective consent, or inability to read and understand English.

2.2. Experimental design

We planned to randomize 28 adults with LOPD 1:1 in blocks of four to 12 weeks of RMT (treatment) or sham-RMT (control) to accommodate a 20% dropout rate. Power analysis was based on our preliminary research of RMT in LOPD for the treatment group in which we observed a mean change in MIP of 8.6 cmH_2O (5.0) [14] and assumed a mean change in MIP of 1.0 cmH_2O (3.2) in the control arm. The power for this study to detect significant differences between groups at alpha = 0.05 was > 90% for both 10 and 12 subjects per study arm. Participants and all researchers, except for the clinician providing RMT therapy (the "RMT clinician"), were blinded to group assignment.

2.3. Procedures

Study participation involved 9 visits to a single tertiary care center (Duke University Medical Center) over approximately 9 months (Fig. 1). Assessments were conducted at pretest, posttest, and after 3- and 6- months detraining.

The primary outcome measure was pretest to posttest change in MIP (in cm H_20). Secondary outcome measures included pretest to posttest changes in: MEP (in cm H_20); peak cough flow (PCF, L/s); ultrasound measures of the diaphragm including resting thickness (in mm) and thickening ratio (maximal thickness upon deep inhalation/maximal resting thickness); 6-Minute Walk Test (6MWT, in m); Gait,

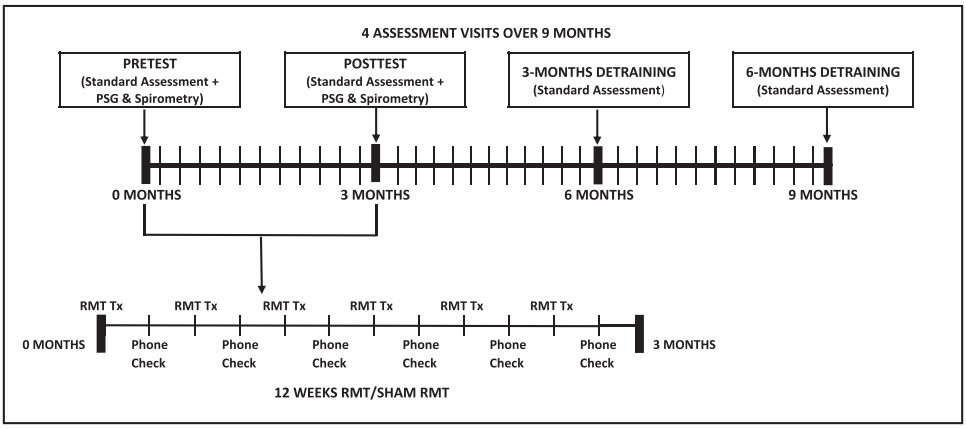

Fig. 1. **Study Overview.** PSG = polysomnography, RMT Tx = on-site RMT or sham therapy visits, Phone Check = telephone contact with RMT clinician.

Stairs, Gowers, Chair scale (GSGC) qualitative total score and time required to complete each of four activities (in s): walking 10 m, climbing 4 steps, rising to standing from supine, and rising to standing from sitting in a chair; and Rasch-built Pompe-specific Activity scale (R-PACT) score. Exploratory outcome measures included polysomnography (PSG) data from participants without nocturnal noninvasive ventilation, as the use of noninvasive ventilation may confound the results. Other exploratory outcomes obtained included patient-reported outcomes of fatigue (Fatigue Severity Scale [FSS]), daytime sleepiness (Epworth Sleepiness Scale [ESS]), and sleep quality (Pittsburgh Sleep Quality Index [PSQI]). Detraining data, from posttest to 3- and 6-month follow-up are also included for primary and secondary outcome measures, as well as patient-reported outcome measures.

Participants were randomized after pretest and RMT or sham-RMT was initiated. During the 12-week intervention period, participants in both arms participated in six RMT therapy sessions in the research lab of the PI every other week and completed a home-based RMT/sham-RMT program. Participants were instructed to complete 75 repetitions each for both inspiratory and expiratory RMT/sham-RMT 5 days per week. In total, participants were prescribed 4500 inspiratory and 4500 expiratory repetitions over the 12-week intervention.

Subjects in both arms completed RMT with pressure-threshold devices that used a spring-loaded valve to provide resistance training against inspiration and expiration, independent of respiratory flow rate. As previously described [13-15], we employed commercially available RMT devices that we modified in specific ways to serve our research needs and were calibrated to provide accurate resistance based on each individual's MIP and MEP according to treatment allocation. To provide access to calibrated inspiratory and expiratory pressure-thresholds across the range of human performance, custom adapters were developed for the EMST 150 and Threshold PEP to allow the delivery of inspiratory pressure-threshold resistance with these devices [15]. In addition, we employed the RMT Monitor, a novel tool which automated data collection, enhanced control over RMT dose, and provided user biofeedback after each repetition [15].

Participants in the treatment arm performed inspiratory and expiratory RMT repetitions at a calibrated, individualized pressure-threshold equal to 70% of their MIP (for inspiratory training) and MEP (for expiratory training). If RMT repetitions were not well-tolerated or successfully achieved per our standard criteria, resistance was decreased in 10% increments of MIP/MEP to a minimum of 50%. Control subjects performed inspiratory and expiratory sham-RMT repetitions at a calibrated, individualized pressure-threshold equal to 15% of their MIP (for inspiratory training) and MEP (for expiratory training).

Instructions for the home-based RMT/sham-RMT program were provided at the conclusion of each RMT therapy session. The RMT Monitor recorded the number of RMT repetitions attempted and successfully completed and adherence data were downloaded and reviewed with participants during each RMT therapy visit.

2.4. Data analysis

Data are presented as the mean ± SD. Primary analysis was conducted according to the intention-to-treat (ITT) principle in which all participants with at least 80% adherence were included, regardless of final study completion. ITT analysis included all 22 subjects randomized to the treatment or control groups. Categorical demographic characteristics (e.g., gender, race) are summarized using counts and percentages; the differences in these variables by treatment arms are examined using Chi-squared tests or Fishers exact test. Continuous demographic, primary, secondary, and exploratory variables are summarized using means, standard deviations (SD) and quartiles. Differences by treatment arms for these variables are examined using Wilcoxon tests as all these variables are non-normal. The primary, secondary, and exploratory variables are examined without adjustment for multiple comparisons at alpha = 0.05. All data analysis is performed with SAS 9.4 statistical software (SAS Institute Inc., Cary, NC).

2.5. Safety monitoring

The PI graded the severity of adverse events using the Common Toxicity Criteria and employed a scale to attribute the relatedness of the experience to the study procedures/interventions (i.e., definitely related, probably related, possibly related, probably not related, and definitely not related). Guidelines for determining which study-related events qualified as mild, moderate, or severe were developed prior to the start of the study. Transient elevated pain or effort ratings or mild and transient shortness of breath, dizziness, or fatigue that resolved with the subject's own modifications (increased rest breaks, slowed pace, etc.) were classified as mild adverse events, not requiring treatment. Pain ratings $\geq$ 4 or effort ratings $\geq$ 8 that resolved in $<$ 48 h with modifications to treatment intensity (pressure threshold or number of repetitions/day) and/or behavioral modifications (increased rest breaks, slowed pace) directed by RMT clinician as per the study protocol, were classified as moderate adverse events, resolving with treatment. Severe adverse events included any incident that resulted in inability to carry on normal activities and required professional medical attention. RMT-related severe adverse events included any pain rating $\geq$ 4 or effort rating $\geq$ 8 not resolving within 48 h following modifications to treatment intensity and/or behavioral modifications. Guidelines for determining adverse event relatedness were also developed prior to the start of the study. Intermittent thoracic pain $\geq$ 4 occurring only during RMT or effort ratings $\geq$ 8 with RMT (i.e., events with clear temporal association) was defined as "definitely related." Continuous thoracic pain $\geq$ 4 in the absence of other mitigating circumstances (recent car accident, unusual exertion during daily activities) was defined as "probably related." Events with clear lack of relational or temporal association with RMT (e.g., hospitalization following an appendectomy or car accident, minor sickness not related to RMT that prevented the participant from completing RMT repetitions) were defined as "definitely not related."

3. Results

Twenty-eight subjects with LOPD were enrolled in the study. Six subjects withdrew before starting study procedures due to concerns about the time and/or expense of the required travel or their overall health status. Therefore 22 subjects were randomized to either RMT ($n=12$) or sham-RMT ($n=10$) and completed the treatment phase of the study. Baseline characteristics for these 22 participants are provided in Table 1. Data are presented as pretest-posttest mean change scores (standard deviation).

Table 1
Pretest subject characteristics. ERT=enzyme replacement therapy, MIP=maximum inspiratory pressure, MEP=maximum expiratory pressure, FVC=forced vital capacity. Data are presented as mean (SD).

	RMT ($n=12$)	Sham-RMT ($n=10$)	P-value
Age (years)	53.2 (12.7)	46.6 (13.9)	0.2754
Gender	$M=3$ $F=9$	$M=6$ $F=4$	0.1128
Ethnicity	White=12	White=9 AA=1	0.3153
Age at diagnosis (years)	52.5 (0.5)	52.5 (0.5)	0.7666
Time on ERT (years)	6.1 (3.1)	3.3 (3.0)	0.0265*
MIP Percent Predicted	55.4 (20.8)	69.9 (31.2)	0.2353
MIP (in cm H20)	44.3 (15.4)	63.6 (31,5)	0.1289
MEP Percent Predicted	66.3 (25.5)	74.7 (30.3)	0.6642
MEP (in cm H20)	61.3 (19.8)	83.0 (28.0)	0.0695
Upright FVC (liters)	2.1 (0.6)	2.9 (1.4)	0.2351
Supine FVC (liters)	1.4 (0.6)	2.3 (1.5)	0.2597
Nocturnal breathing support	None=5 CPAP=2 BiPAP=1 AVAPS=4	None=4 CPAP=1 BiPAP=5 AVAPS=0	0.6774
Ambulatory status	Independent=5 Cane/Walker=6 Wheelchair=1	Independent=7 Cane/Walker=2 Wheelchair=1	0.2822

3.1. Primary/Secondary dependent variables: Pretest to posttest

Data for pretest to posttest change scores for primary and secondary outcomes for are presented in Table 2 and Fig. 2**.** MIP increased 7.6 cmH_2O (15.9) in the treatment group and 2.7 cmH_2O (7.6) in the control group ($P=0.4670$). MEP increased 14.0 cmH_2O (25.9) in the treatment group and 0.0 cmH_2O (12.0) in the control group ($P=0.1854$). PCF increased 0.4 L/s (1.8) in the treatment group and 0.7 L/s (2.3) in the control group ($P=0.5528$). On ultrasound measures, diaphragm thickness at rest decreased 0.2 mm (0.9) in the treatment group and 0.2 mm (0.9) in the control group ($P=0.9292$) while diaphragm thickening ratio increased 0.1 (0.2) in the treatment group and 0.2 (0.2) in the controls ($P=0.3011$).

Distance walked in 6MWT increased 22.0 m (28.8) in the treatment group and 9.8 m (20.1) in the control group ($P=0.3390$). R-PACT score decreased 0.1 (2.3) in the treatment group and 0.1 (2.1) in the control group ($P=0.9733$). GSGC results were as follows. On the Gait subtest, time to walk 10 m decreased 0.5 s (1.2) in the treatment group and 0.7 s (1.5) in the control group ($P=0.7666$). On the Stair subtest, time to climb 4 steps decreased 0.9 s (1.0) in the treatment group and 0.1 s (0.9) in the control group ($P=0.0346$). On the Gower's maneuver subtest, time to rise from floor to standing increased 0.3 s (1.3) in the treatment group and 0.8 s (1.2) in the control group ($P=0.2714$). On the Chair subtest, time to stand from seated decreased 1.1 s (2.1) in the treatment group and 0.2 s (1.5) in the control group ($P=0.1299$). GSGC Qualitative Total Score decreased 0.8 (1.0) in the treatment group and 0.1 (1.1) in the control group ($P=0.1499$).

3.2. Exploratory outcomes: Pretest to posttest

We found no statistically significant pretest to posttest changes in polysomnography outcomes without noninvasive ventilation (Table 3). Pretest to posttest change in patient-

Table 2
Pretest to posttest change in primary and secondary outcomes. MIP=maximum inspiratory pressure, MEP=maximum expiratory pressure, PCF=peak cough flow, 6MWT=6-minute walk test, GSGC=Gait Stairs Gowers and Chair, R-PACT=Rasch-built Pompe-specific activity scale. Note (-) represents improvement for GSGC Total Score and timed functional tests. Data are presented as mean (SD).

Outcome	RMT ($n=12$)	Sham-RMT ($n=10$)	P-value
MIP (in cm H_20)	+7.6 (15.9)	+2.7 (7.6)	0.4670
MIP (% predicted)	+9.2 (19.4)	+2.2 (8.1)	0.4678
MEP (in cm H_20)	+14.0 (25.9)	+0.0 (12)	0.1854
MEP (% predicted)	+14.3 (27.6)	−0.5 (12.9)	0.1557
PCF (in L/s)	+0.4 (1.8)	+0.7 (2.3)	0.5528
Diaphragm thickness at rest (in mm)	−0.2 (0.9)	−0.2 (0.9)	0.9292
Diaphragm thickening ratio	+0.2 (0.2) [$n=10$]	+0.1 (0.2) [$n=8$]	0.3011
6MWT (in m)	+22.0 (28.8)	+9.8 (20.1)	0.3390
R-PACT	−0.1 (2.1)	−0.1 (2.3)	0.9733
GSGC Gait subtest (time to walk 10 m, in s)	−0.5 (1.2)	−0.7 (1.5)	0.7666
GSGC Stair subtest (time to climb 4 steps, in s)	−0.9 (1.0) [$n=11$]	−0.1 (0.9) [$n=10$]	0.0346*
GSGC Gower's maneuver subtest (time to rise from floor to standing, in s)	+0.3 (1.3) [$n=8$]	+0.8 (1.2) [$n=8$]	0.2714
GSGC Chair subtest (time to rise from chair, in s)	−1.1 (2.1) [$n=11$]	−0.2 (1.5) [$n=10$]	0.1299
GSGC Qualitative Total Score	+0.8 (1.1)	+0.1 (1.1)	0.1752

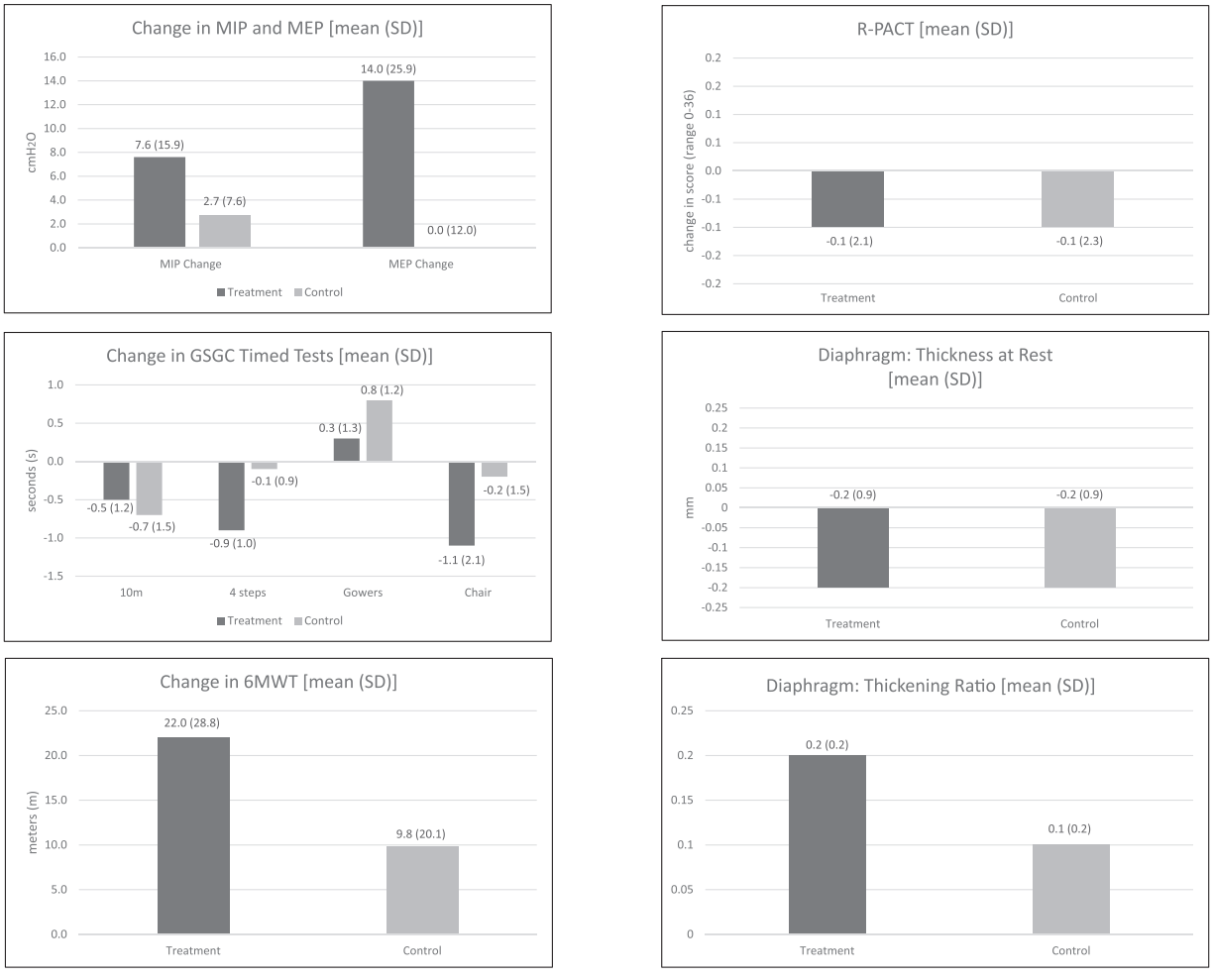

Fig. 2. Pretest to posttest change in primary and secondary outcomes. Data are presented as mean (SD). MIP=maximum inspiratory pressure; MEP=maximum expiratory pressure; GSGC=Gait, Stairs, Gowers, Chair; 6MWT=6-minute walk test; R-PACT=Rausch-built Pompe-specific Activity Scale.

Table 3
Pretest to posttest change in polysomnography outcomes without nocturnal ventilation. TcCO2= transcutaneous carbon dioxide; SaO2=oxygen saturation; AHI TST=Apnea-Hypopnea Index; TST=total sleep time; REM=rapid eye movement; NREM=non-REM sleep; ODI=oxygen desaturation index; RERA=respiratory effort-related arousal; PLM=periodic limb movement; RDI=respiratory disturbance index; N1-N3=stages of NREM sleep. Data are presented as mean (SD).

Outcome	RMT ($n=7$)	Sham-RMT ($n=3$)	*P*-value
Peak TcCO2	−11.7 (19.9)	0.7 (4.6)	0.1583
SaO2 nadir	0.3 (5.0)	−1.3 (2.5)	0.9076
AHI TST	−4.7 (15.6)	1.0 (6.2)	1.0000
AHI REM	9.4 (9.1)	−6.3 (10.0)	0.0674
AHI NREM	−6.7 (15.6)	2.0 (7.0)	0.3545
ODI	−1.2 (13.7)	3.0 (1.6)	0.8197
Arousal index	−3.0 (10.5)	4.7 (1.2)	0.4915
RERA	−1.8 (4.1)	0.4 (5.9)	1.0000
PLM Index	2.3 (6.2)	0.8 (4.7)	0.8197
RDI	−6.5 (19.4)	1.4 (12.1)	1.0000
Sleep efficiency	−1.3 (13.4)	−11.0 (10.5)	0.4222
N1	1.0 (4.9)	3.7 (4.0)	0.5664
N2	−5.1 (12.2)	−1.0 (14.0)	0.7309
N3	−2.0 (10.1)	−1.7 (13.3)	1.0000

Table 4
Pretest to posttest change in patient-reported outcomes of fatigue (FSS), daytime sleepiness (ESS), and sleep quality (PSQI). FSS=Fatigue Severity Scale, ESS=Epworth Sleepiness Scale, PSQI=Pittsburgh Sleep Quality Index. Data are presented as mean (SD).

Outcome	RMT ($n=12$)	Sham-RMT ($n=10$)	*P*-value
FSS	+1.7 (5.5)	−1.3 (3.3)	0.0984
ESS	−1.2 (2.4)	+1.1 (2.0)	0.0160
PSQI	−0.3 (4.6)	−0.7 (2.3)	0.8677

reported outcomes of fatigue (FSS), daytime sleepiness (ESS), and sleep quality (PSQI) are shown in Table 4 (note, a decrease in score represents improvement for these outcomes). FSS score increased 1.7 (5.5) in the treatment group and decreased 1.3 (3.3) in the control group ($P=0.0984$). ESS score decreased 1.2 (2.4) in the treatment group and increased 1.1 (2.0) in the control group ($P=0.0160$). PSQI score decreased 0.3 (4.6) in the treatment group and 0.7 (2.3) in the control group ($P=0.8677$).

3.3. Detraining data

Detraining data for posttest to 3- and 6-month follow up for primary and secondary outcomes are presented as change scores as seen in Tables 5 and 6. Note one participant in the RMT group withdrew from the study after completing the posttest visit. Withdrawal was due to declining health status that prevented the participant from traveling to complete the two detraining visits.

3.4. Secondary analysis

A per protocol analysis, including only participants who complied with the trial protocol, was also completed and two subjects were excluded; one subject in the treatment group changed ERT dose during the intervention and one subject in the control group had difficulty following instructions during assessment visits. This did not alter study results.

3.5. Treatment dose

3.5.1. Adherence

The mean adherence rate was 98% (SD=5.0) in the treatment arm and 97% (5.1) in the control arm.

3.5.2. Pressure-threshold resistance

Subjects in the treatment arm completed inspiratory repetitions at mean values equal to 60% (8.3) and 62% (7.8) of MIP and MEP, respectively. All subjects in the control arm completed inspiratory and expiratory repetitions at 15% of MIP and MEP.

3.5.3. Rating of perceived effort

Subjects in both treatment and control groups made ratings of perceived effort using a 0–10 scale after RMT sets. Mean rating of perceived effort for inspiratory repetitions was 5.6 (1.1) in the treatment group and 3.5 (1.8) in the control group. Mean rating of perceived effort for expiratory repetitions was 5.6 (1.2) in the treatment group and 3.7 (1.6) in the control group.

3.6. Safety

A total of twenty-one adverse events occurred: 20 in the treatment group and one in the control group (see Table 7). In terms of their severity, two were severe, nine were moderate, and ten were mild. No participants were discontinued from intervention due to an adverse event.

4. Discussion

The primary outcome for this exploratory, double-blind, sham-controlled RCT of RMT in LOPD was pretest to posttest change in MIP. Although change in MIP was greater in the treatment group versus control, these differences did not achieve statistical significance. Similarly, while pretest to posttest change in MEP was greater in the treatment group relative to control, these differences were not statistically significant. Except for pretest to posttest improvements in time to climb 4 steps on the GSGC Stairs subtest and decreased daytime sleepiness based on ESS results, we did not find statistically significant between group differences on our other secondary and exploratory outcomes.

Explanations for these findings include insufficient power because of larger than expected variability. Power analysis for the treatment group in this trial was based on our preliminary research of RMT in LOPD in which we observed a mean change in MIP of 8.6 cmH_2O (5.0) [14]. Assuming a mean change in MIP of 1.0 cmH_2O (3.2) in the control arm, the power for this study to detect significant differences between groups at alpha=0.05 was > 90% for both 10 and 12 subjects

Table 5
Posttest to 3-month follow up change in primary and secondary outcomes. MIP=maximum inspiratory pressure, MEP=maximum expiratory pressure, PCF=peak cough flow, 6MWT=6-minute walk test, GSGC=Gait Stairs Gowers and Chair, R-PACT=Rasch-built Pompe-specific activity scale. Note (-) represents improvement for GSGC Total Score and timed functional tests. Data are presented as mean (SD).

Outcome	RMT ($n=11$)	Sham-RMT ($n=10$)	P-value
MIP (in cm H_20)	−0.9 (7.1)	+1.4 (6.1)	0.5252
MIP (% predicted)	−1.0 (8.9)	+2.4 (7.0)	0.5034
MEP (in cm H_20)	−2.6 (11.3)	−2.0 (11.2)	0.4589
MEP (% predicted)	−2.8 (12.0)	−0.3 (12.2)	0.6985
PCF (in L/s)	−0.6 (1.1)	+ 0.1 (0.8)	0.2453
Diaphragm thickness at rest (in mm)	−0.2 (0.5)	−0.1 (0.5)	0.8099
Diaphragm thickening ratio	0.0 (0.5)	−0.1 (0.4)	0.7724
6MWT (in m)	−10.0 (11.7)	−28.3 (97.6)	0.5035
R-PACT	−0.2 (1.3)	−0.9 (1.9)	0.5251
GSGC Gait subtest (time to walk 10 m, in s)	+0.3 (1.3)	+0.6 (1.5)	0.5949
GSGC Stair subtest (time to climb 4 steps, in s)	+0.2 (1.3)	0.0 s (1.1)	0.9159
GSGC Gower's maneuver subtest (time to rise from floor to standing, in s)	−1.3 (3.7)	+0.1 (1.5)	0.4345
GSGC Chair subtest (time to rise from chair, in s)	−0.5 (2.0)	+0.8 (3.2)	0.9025
GSGC Qualitative Total Score	0.5 (0.7)	0.3 (1.6)	0.1685

Table 6
Posttest to 6-month follow up change in primary and secondary outcomes. MIP=maximum inspiratory pressure, MEP=maximum expiratory pressure, PCF=peak cough flow, 6MWT=6-minute walk test, GSGC=Gait Stairs Gowers and Chair, R-PACT=Rasch-built Pompe-specific activity scale. Note (-) represents improvement for GSGC Total Score and timed functional tests. Data are presented as mean (SD).

Outcome	RMT ($n=11$)	Sham-RMT ($n=10$)	P-value
MIP (in cm H_20)	−3.4 (12.7)	+1.0 (5.6)	0.5252
MIP (% predicted)	−4.0 (15.6)	+1.6 (6.3)	0.3979
MEP (in cm H_20)	−3.4 (16.2)	−2.1 (8.5)	0.3233
MEP (% predicted)	−3.3 (17.2)	−0.7 (7.9)	0.4181
PCF (in L/s)	−0.4 (1.0)	+0.1 (0.6)	0.6984
Diaphragm thickness at rest (in mm)	+0.0 (0.6)	+0.5 (1.3)	0.4134
Diaphragm thickening ratio	−0.1 (0.7)	−0.2 (0.6)	1.0000
6MWT (in m)	−21.6 (17.9)	+4.2 (27.0)	0.0528
R-PACT	−0.5 (2.0)	+0.2 (1.3)	0.5439
GSGC Gait subtest (time to walk 10 m, in s)	+0.5 (2.2)	+0.9 (1.9)	0.4597
GSGC Stair subtest (time to climb 4 steps, in s)	+0.0 (0.9)	+0.1 (0.9)	0.6220
GSGC Gower's maneuver subtest (time to rise from floor to standing, in s)	+0.0 (3.6)	−0.1 (1.6)	0.7645
GSGC Chair subtest (time to rise from chair, in s)	−1.1 (3.2)	+1.2 (3.4)	0.3642
GSGC Qualitative Total Score	+0.4 (0.7)	−0.6 (1.6)	0.1081

Table 7
Description of adverse events recorded during the study (21 events in 11 participants). RMT=respiratory muscle training, ADLs=activities of daily living.

Severity	Relatedness	Description of Event (*Action Taken*)
Mild (10)	Definitely related=5	Headache temporally related to RMT = 2 (*no action taken*)
		RMT-related thoracic pain during home RMT = 2 (*no action taken*)
		Muscle myalgia associated with ADLs causing mild pain during home RMT = 1 (*no action taken*)
	Possibly related=1	Headache not temporally related to RMT = 1 (*no action taken*)
	Definitely not related=4	Fall without injury = 2 (*no action taken*)
		Viral infection = 1 (*no action taken*)
		Increased chronic pain associated with stress/fatigue = 1 (*no action taken*)
Moderate (9)	Definitely related=4	Effort ratings ≥8 with home RMT = 4 (*reduced frequency of home training until resolution*)
	Possibly related=1	Lightheadedness with RMT after taking prescription medication for vertigo = 1 (*increased rest breaks during RMT repetitions)*
	Probably not related=1	Rectal bleeding = 1 (*no action taken*)
	Definitely not related=3	Fall without injury = 2 (*no action taken*)
		Elevated blood pressure = 1 (*MD notified, evaluation postponed to next day*)
Severe (2)	Definitely not related=2	Respiratory infection requiring hospitalization = 1 (Control) (*no action taken*)
		Inability to travel per MD due to declining health status = 1 (*self-withdrawal from study*)

per study arm. In the current trial, pretest to posttest MIP increased by 7.6 cmH_2O (15.9) in the treatment arm and 2.7 cmH_2O (5.6) in the control arm. In terms of the overall magnitude and durability of change to 3-months detraining, the results in the treatment group are largely consistent with our preliminary research. However, based on the standard deviation of the MIP change scores, variability in response to RMT was greater in the current trial (15.9) than in our preliminary research (8.6). Similarly, in the control group, both the magnitude of change and the variability in response were greater than expected. If we assume the values of mean change and standard deviation in MIP in the treatment and control arms observed in the current study are normally distributed, for 80% power at alpha=0.05, a future two-arm study without adjustment for dropouts would require a total of 190 subjects (95 per arm) and therefore the current RCT was underpowered.

Another possible explanation for these findings were the differences between groups in terms of baseline subject characteristics. Although subjects were randomly assigned to treatment or control arms, those allocated to the treatment were older, had been on enzyme replacement therapy longer, and had increased respiratory muscle involvement in comparison to subjects assigned to the control. Although these differences only achieved statistical significance for time on ERT, differences in baseline subject characteristics suggest that subjects in the treatment group differed from the control group in important ways (e.g., duration of treatment, age, severity of respiratory muscle weakness). One of the aims of this exploratory trial was to determine whether sham-RMT was a useful, feasible control for RMT in LOPD. In this RCT, the first controlled study of RMT in LOPD, sham-RMT facilitated blinding in both researchers and subjects and there was no evidence that researchers or subjects penetrated the blind. Additionally, research participation and adherence was similar across study groups; twenty of 22 subjects completed all study visits and adherence rates were high in both treatment (98% [5.0]) and control (97% [5.1]) arms. However, sham-RMT did not appear to be an inert control. We carefully selected 15% of MIP/MEP for pressure-threshold resistance in sham-RMT subjects to facilitate blinding while providing what was expected to be insufficient resistance to increase respiratory muscle strength based on data in other patient populations [26–28]. However, comparing the effects of sham-RMT in this exploratory trial versus estimates used for power analysis showed that both magnitude of change and variability in response was greater in the control arm than expected. Based on these data, subjects in the control group exhibited an active response to sham-RMT and therefore sham-RMT does not appear to be an optimal control condition for RMT in LOPD.

Other important findings include subject adherence. Our 12-week RMT regimen was intended to be intensive: each subject was prescribed 3 sets of 25 inspiratory repetitions and 3 sets of 25 expiratory repetitions 5x/week for a total of 4500 inspiratory repetitions and 4500 expiratory repetitions per subject. We measured adherence quantitatively using a device developed for use in this trial and despite the relatively demanding RMT regimen we prescribed, adherence rates were very high in both treatment (98%) and control (97%) groups.

Another important finding from this RCT was the apparent safety of the intervention as there were no serious adverse events related to participation. Five moderate adverse events that were definitely or possibly related to study participation occurred, most commonly excessive participant effort with RMT based on subject ratings of perceived effort with RMT $\geq$ 8. Five mild adverse events occurred that were definitely related to study participation, including headache temporally related to RMT and RMT-related thoracic pain. In all cases, these successfully resolved on their own or with modifications to the treatment dose (decrease in frequency of home training until resolution). These safety data provide additional evidence in support of the notion that supervised RMT is safe and well-tolerated in subjects with LOPD.

Overall, despite the lack of statistical significance, the observed magnitude of pretest to posttest change in MIP is consistent with findings from similar, albeit uncontrolled, studies. In the present trial, MIP increased from 44.3 to 51.9 cmH_2O in the treatment group over 12 weeks, a 7.6 cmH_2O change reflecting a 17.2% increase. In our pilot research, we investigated the effect of our 12-week RMT regimen using a single-subject experimental design replicated in 8 adults with LOPD; across participants, pretest to posttest MIP increased by 8.6 cmH_2O or 19.5% [14]. In 2015, Jevnikar and colleagues studied the effects of 24-months of IMT in 8 LOPD subjects; MIP increased by 5.6 cmH_2O or 17.8% [24]. Aslan and colleagues investigated the effects of 8-weeks of IMT in 8 LOPD participants; MIP increased by 9 cmH_2O or 30.0% [23]. More recently, Wenninger and colleagues examined the effects of IMT in 11 LOPD subjects. Over 6-weeks, MIP increased 7.63 cmH_2O or 15.7% [25]. Although there are substantial differences in treatment dose, research design, and methodology among studies of RMT in LOPD, our results in this trial are largely consistent with the work from other researchers which have shown a 15.7 to 30% increase in MIP in response to RMT.

Similarly, our finding that supervised and individualized RMT is safe and well-tolerated is consistent with reports from other researchers. Wenninger and colleagues reported no severe adverse events related to study participation in their 11 subjects [25]. Similar to our own safety monitoring data, mild or moderate adverse events definitely or possibly related to study participants included myalgia of facial muscles in two subjects, myalgia of back muscles in one subject, and headache in one subject. In our preliminary research in 8 LOPD subjects, one subject had an adverse event related to study participation described a “greater than mild thoracic pain” (p. 127) that resolved with treatment [14]. In this subject, the amount of pressure-threshold resistance was not calibrated and was thought to possibly be greater than intended. Additionally, she documented completing more RMT repetitions than prescribed. Other safety data in this area includes the 2016 report from Aslan et al. in which one of

their nine participants discontinued the study due to vertigo [23]. Overall, safety monitoring data from this trial and other research suggest that supervised RMT programs are safe and well-tolerated in LOPD.

Although treatment for LOPD is available in the form of ERT, the effects on respiratory muscle involvement are generally modest [3] and respiratory muscle weakness remains the primary cause of morbidity and mortality [29]. More specifically, respiratory weakness in LOPD leads to progressive respiratory insufficiency, sleep-disordered breathing frequently requiring nocturnal noninvasive ventilation [7], and ineffective cough and reduced airway clearance [6]. Although the results from our trial were not conclusive, our findings as well as those from other researchers continue to suggest a possible role for focused resistance training with RMT to target progressive respiratory weakness in LOPD.

We must acknowledge the limitations of this research. Although this is the largest study of RMT in LOPD conducted to date, we still suffer from a relatively small sample size of 22 participants. As discussed above, this relatively small sample size coupled with greater than expected variability in pretest to posttest MIP change scores likely led to this trial being underpowered for our primary outcome measure.

Between group differences in baseline subject characteristics was another limitation of this study. Despite random assignment, subjects allocated to the treatment group had greater overall disease severity compared to controls. We carefully considered stratifying participants based on disease severity but ultimately elected not to proceed in this fashion due to concerns about the possible negative effects on subject recruitment in this rare disease. However, in future clinical trials of RMT in LOPD utilizing a similar design, we recommend subjects be stratified based on factors such as duration of treatment, age, and severity of respiratory muscle weakness to improve the likelihood of equal distribution of participants across groups.

The use of sham-RMT as a control condition for RMT ultimately also proved to be a limitation in this trial. Although sham-RMT allowed us to conduct a double-blind RCT, our findings suggest that sham-RMT was not an inert control but rather an active treatment. Future research in this area requires consideration of alternative research designs to the double-blind, sham-controlled RCT used in this trial.

Other limitations of this study include the effort-dependent nature of volitional measurements of respiratory muscle strength (i.e., MIP, MEP) and the potential confounder of learning effects on repeat maneuvers across time. Our research protocol was carefully designed to minimize learning effects and maximize reproducibility of measures of MIP and MEP. Additionally, it is established that MIP is highly correlated with invasive measures of volitional and reflexive inspiratory strength such as transdiaphragmatic pressure during sniff and maximal inspiratory maneuvers and magnetic phrenic nerve stimulation in patients with LOPD [30]. Additionally, MIP is increasingly recognized as both an important measure of respiratory muscle function and a clinically meaningful study endpoint in patients with chronic neuromuscular disease [31]. Although FVC has been used as an estimate of overall respiratory function in prior clinical trials in LOPD [3,8] there are several limitations to its use. For example, as an indirect measure of respiratory muscle strength, FVC is relatively insensitive to changes in respiratory muscle strength [31,32] due to the curvilinear shaped relationship of the lung pressure-volume curves [33]. Therefore, in comparison to MIP, FVC may be suboptimal to detect changes in respiratory muscle function, especially early changes [34–36]. In other words, substantial decreases in respiratory muscle strength may be present before reductions in lung volume measures like FVC are affected [37].

Finally, the nature of our randomized, double blind study design likely had unanticipated consequences for delivery of the intervention. For example, strict adherence to written scripts when shaping RMT repetitions, providing feedback, and responding to participants' questions may have limited the RMT clinician's ability to effectively deliver a behavioral treatment like RMT.

Although one of our aims for this trial was to determine the clinically meaningful secondary and exploratory outcomes for inclusion in future research, our statistical analysis did not allow us to determine which outcomes should be retained in future trials of RMT in LOPD. However, our experience in this trial suggests there were clear limitations for our exploratory outcome PSG data. Most of our participants used nocturnal breathing support at baseline and these subjects were generally not comfortable completing even a portion of the PSG off support, making the collection of meaningful PSG data very challenging. In total, PSG data were obtained in only ten participants: seven in the treatment arm and three in the control arm. Considering the limited value of these data, as well as the substantial participant burden and research financial cost, PSG outcomes do not appear to merit inclusion in future studies of RMT in LOPD utilizing a similar protocol. The use of continuous overnight transcutaneous CO_2 monitoring may be an alternative approach to evaluate nocturnal hypoventilation.

Further controlled research regarding the role of RMT in LOPD is necessary and it is evident that such trials will require a larger sample size. Considering the challenges inherent in research in rare disease, such efforts will likely necessitate multisite trials. Multisite trials with a greater number of participants will also facilitate subgroup analysis to improve understanding of the baseline subject characteristics that may influence response to RMT. As noted above, if future research studies utilize a double-blind RCT research design similar to this trial, stratification of participants based on estimates of overall disease severity or respiratory muscle involvement will likely be needed. Finally, future investigations must carefully consider the research design to be used, including the control condition. Alternative designs, such as a no-treatment waiting period control, warrant further consideration for future trials.

5. Conclusion

Results from this exploratory, double-blind, sham-controlled RCT of RMT in LOPD show promise for treatment of respiratory weakness and warrant further investigation. With very few treatment options available for respiratory muscle weakness in this population, our findings confirm our prior experiences suggesting our 12-week RMT regimen is safe and well-tolerated in LOPD subjects. In terms of magnitude of change, changes in MIP and MEP were consistent with our pilot findings but did not achieve statistical significance. Explanations for this include insufficient power due to greater than expected variability and baseline differences between groups in terms of subject characteristics despite randomization. The results confirm that patients with LOPD are highly motivated to participate in relevant clinical research and provide key insight for design of a rigorous future multi-site trial.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

LEC, PSK, LHW, and HNJ have received research/grant support and honoraria from Sanofi Genzyme Corporation. LEC is a member of the Pompe Registry Board of Advisors for Sanofi Genzyme. PSK has received research/grant support, honoraria, and/or consulting fees from Valerion Therapeutics, Amicus Therapeutics, Vertex Pharmaceuticals, and Asklepios BioPharmaceuticals, Inc; is a member of the Pompe and Gaucher Disease Registry Advisory Board for Sanofi Genzyme, Amicus Therapeutics, and Baebies; and has equity in Actus Therapeutics. HNJ has US Patent applications for respiratory muscle training-related intellectual property licensed by Aspire LLC and is a paid consultant for Aspire LLC. LHW receives consulting fees from Wiley Publishing for work as an Associate Editor of Muscle and Nerve. MK, KDC, MTB, JAM, and RMK have no conflicts of interest to report.

Acknowledgements

This work was supported by the National Institutes of Health, the National Institute of Arthritis and Musculoskeletal and Skin Diseases [R21AR069880]. The authors would like to acknowledge Joanna Downer for her helpful discussions and editorial guidance, Emily Randolph and Tracy Boggs for their contributions to data collection, and Matt Brown for his contributions to the development and production of the RMT-related technologies described in this manuscript. Additionally, we would like to thank all past and future participants in our research and express our gratitude to the members of our invaluable Patient Advisory Committee.

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