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Training, detraining, and retraining: Two 12-week respiratory muscle training regimens in a child with infantile-onset Pompe disease

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Abstract.
BACKGROUND: Respiratory muscle weakness is a primary cause of morbidity and mortality in patients with Pompe disease. We previously described the effects of our 12-week respiratory muscle training (RMT) regimen in 8 adults with late-onset Pompe disease [1] and 2 children with infantile-onset Pompe disease [2].
CASE REPORT: Here we describe repeat enrollment by one of the pediatric participants who completed a second 12-week RMT regimen after 7 months of detraining. We investigated the effects of two 12-week RMT regimens (RMT #1, RMT #2) using a single-participant A-B-A experimental design. Primary outcome measures were maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP). Effect sizes for changes in MIP and MEP were determined using Cohen's d statistic. Exploratory outcomes targeted motor function.
RELEVANCE: From pretest to posttest, RMT #2 was associated with a 25% increase in MIP and a 22% increase in MEP, corresponding with very large effect sizes ($d = 2.92$ and $d = 2.65$, respectively). Following two 12-week RMT regimens over 16 months, MIP increased by 69% and MEP increased by 97%, corresponding with very large effect sizes ($d = 3.57$ and $d = 5.10$, respectively). MIP and MEP were largely stable over 7 months of detraining between regimens. Magnitude of change was greater for RMT #1 relative to RMT #2.

Keywords: Pompe disease, glycogen storage disease type II, skeletal muscle, neuromuscular disease, rehabilitation, respiratory muscle training

Abbreviations

RMT:	Respiratory Muscle Training
IOPD:	Infantile-Onset Pompe Disease
LOPD:	Late-Onset Pompe Disease
MIP:	Maximum Inspiratory Pressure
MEP:	Maximum Expiratory Pressure
ERT:	Enzyme Replacement Therapy
IMT:	Inspiratory Muscle Training
EMT:	Expiratory Muscle Training
6MWT:	6-Minute Walk Test
TFTs:	Timed Functional Tests
PCF:	Peak Cough Flow

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1. Introduction

Pompe disease (glycogen storage disease type II, acid maltase deficiency) is a progressive metabolic myopathy resulting from deficiency of the lysosomal enzyme acid alpha glucosidase (GAA). The most severe phenotype is classic infantile-onset Pompe disease (IOPD) which results from a complete or almost complete absence of GAA. Onset is within the first days to weeks of life and signs and symptoms in-

clude hypertrophic cardiomyopathy, hypotonia, profound muscle weakness, motor delays, feeding difficulties, and respiratory insufficiency [3,4]. Without treatment, death due to cardiorespiratory failure occurs by 24 months of age [5].

Relatively few options are available for the treatment of respiratory muscle weakness. The advent of enzyme replacement therapy (ERT) with alglucosidase alfa in 2006 (Myozyme$^{\mathrm{TM}}$) has improved both overall and ventilator-free survival for children with IOPD [6–9]. Variability exists in individual response to ERT, and appears to arise from multiple factors such as age at initiation of ERT, disease severity, genotype, and immunologic differences [5,9,10]. The first cohort of children with IOPD treated with ERT are now surviving into late adolescence, and implementation of newborn screening (NBS) programs in the US and other countries is reducing diagnostic delay and time to initiation of treatment [11]. Thus, the phenotype of long-term survivors continues to develop. While the need for invasive or noninvasive ventilation has decreased with earlier diagnosis and initiation of treatment [5,9], respiratory muscle weakness persists in some children with IOPD despite treatment with ERT and may result in hypoventilation, reduced cough strength, and reduced tolerance of physical activity [2,10,12–15].

Our laboratory has pioneered the use of respiratory muscle training (RMT) as a treatment for inspiratory and expiratory muscle weakness in individuals with Pompe disease. RMT is accomplished using handheld respiratory trainer devices that provide calibrated, individualized, and progressive pressure-threshold resistance against inhalation (inspiratory muscle training [IMT]) and exhalation (expiratory muscle training [EMT]) [16–20]. We first described the use of a clinical RMT program in two adults with late-onset Pompe disease (LOPD) and severe respiratory muscle weakness [18]. RMT was well-tolerated and large increases in inspiratory and expiratory muscle strength were detected. These observations spurred systematic research to determine the effects of our 12-week RMT regimen using a single-subject experimental design replicated across participants. Participants in this 6-month study, including two childhood survivors of IOPD [2] and eight adults with late-onset Pompe disease (LOPD) [1], completed 12 weeks of RMT and were followed for 3 months of detraining. The primary outcome measures were maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP). These outcomes were assessed at pretest, posttest, and post-detraining, with the magnitude of change estimated using Cohen's d statistic [21].

From pretest to posttest, all 8 adult participants demonstrated increases in MIP and 7 of 8 showed increases in MEP. Effect size data revealed the magnitude of change to be large to very large using conservative estimates. Across participants, pretest to posttest MIP and MEP increased by 19.6% and 16.1%, respectively. Increases in respiratory strength, particularly in terms of the inspiratory muscles, were generally durable to 3-months detraining [1]. In our two pediatric participants, one child demonstrated negligible to modest increases in MIP/MEP (6% increase in MIP, $d = 0.25$; 19% increase in MEP, $d = 0.87$), while the other participant demonstrated very large increases in MIP/MEP (46% increase in MIP, $d = 2.40$; 83% increase in MEP, $d = 4.33$). Following three-month RMT withdrawal, both pediatric participants maintained these strength increases and demonstrated maximal MIP and MEP values at follow-up [2].

We now report additional data from one of our pediatric participants who re-enrolled in the study and completed our 12-week RMT regimen for a second time. Although this participant made significant gains in response to training, she continued to demonstrate respiratory muscle weakness, particularly of the inspiratory muscles. Therefore, 4 months after completing the first 12-week RMT regimen, we offered her and her parents the opportunity to re-enroll in the research to determine if additional increases in respiratory muscle strength could be achieved with additional RMT.

We hypothesized that: 1) additional increases in inspiratory and expiratory strength would be achieved with additional RMT, 2) respiratory strength increases would be at least large in magnitude ($d \geqslant 1.00$), and 3) peak MIP and MEP values over this participant's entire participation would be achieved at posttest following the second course of RMT.

2. Materials and methods

The study was approved by the Duke University Institutional Review Board, and written informed consent was obtained from the participant's parents after explaining the purpose and procedures of the study. This study was part of a larger investigation into the effects of RMT on respiratory muscle strength in participants with Pompe disease. Data from 2 participants with IOPD and 8 adults with LOPD were previously published [1,2].

This report details the response of one of the 2 participants with IOPD following completion of a second

12-week regimen of RMT (RMT #2). The participant was recruited through the Duke Pompe Disease Clinical and Research Program. Inclusion criteria included confirmed diagnosis of Pompe disease via enzyme activity showing deficient GAA activity (skin fibroblasts, muscle, or dried blood spot assay) and mutation analysis showing two GAA gene mutations; ability to participate in an intensive RMT program; and ability to maintain a consistent amount of non-research related physical activity over the course of the study. Exclusion criteria included inability to perform the research protocol; medical problems that precluded meaningful study participation; inability to perform high-effort respiratory tasks; and profound respiratory weakness that would prevent RMT at the minimum pressure-threshold resistance offered by commercially available, FDA-approved RMT devices.

2.1. Participant

The participant was a white female who began ERT infusions at 7 months of age at 20 mg/kg every other week. At 21 months of age, she began receiving infusions at 20 mg/kg every week. The participant was 5 years, 9 months old at the start of 6-months participation in the first 12-week RMT regimen (RMT #1). Seven months after completing the first 12-week regimen of RMT, at age 6 years, 7 months, the participant assented and the participant's parents consented to re-enroll in the study and complete a second course of RMT. Overall, she participated in two 6-month RMT research studies over a 16-month period, each involving 12 weeks of RMT and 3-months detraining (Fig. 1). The participant's ERT regimen and all other aspects of her care remained consistent throughout her participation in RMT research, including ongoing physical therapy. The participant primarily used a wheelchair for mobility, but was able to ambulate with the assistance of a walker and bilateral ankle-foot orthoses (AFOs).

2.2. Experimental design

We used an A-B-A single-participant experimental design in order to allow for statistical analysis of effect size while controlling for threats to internal and external validity [22–24]. The first A phase represents pre-RMT function (pretest), the B phase represents the 12-week RMT program, and the second A phase represents post-RMT function following 12 weeks of detraining (posttest to post-detraining). MIP and MEP were the primary dependent variables and were selected due to their non-invasive nature and high correlation with invasive measures of respiratory strength [25]. Assessments were completed at pretest, posttest, and after 3-months detraining (post-detraining). Effect sizes were calculated using Cohen's d to compare MIP and MEP at each of the three assessment points [21]. Additional exploratory data were also obtained at each assessment to assess the effects of RMT on motor function, including the 6-minute walk test (6MWT) [26], timed function tests (TFTs) [27] and volitional peak cough flow (PCF).

2.3. Procedures

Procedures for RMT #2 were identical to those previously described in detail for RMT #1 [2]. A brief summary of procedures is provided below.

2.3.1. Measurement of primary dependent variables

Procedures for measurement of MIP and MEP followed established guidelines [28,29]. Pretest and posttest assessments were each completed over 2 consecutive days; post-detraining assessments were completed in 1 day. Each day of assessment involved 4 discrete MIP/MEP test sessions comprising repeated measurements of both maneuvers with 30-minute rest periods between each test session. MIP and MEP values from each test session were comprised of the mean of the 3 best efforts produced with $\leqslant 10\%$ variability. Test equipment included a calibrated digital pressure gauge (RPM-001, Micro Direct; Lewistown, PA, USA), flanged mouthpiece, and nose clips. MIP was performed from forced residual volume and MEP was calculated from total lung capacity. [28].

2.3.2. Other assessment procedures

At pretest, a pulmonologist with expertise in Pompe disease (RK) interviewed the participant and her family, completed a physical exam, and interpreted spirometry results to ensure medical optimization for safe and meaningful study participation. We selected our exploratory outcomes to assess the effects of increases in respiratory strength on motor function and volitional cough. At pretest, posttest, and post-detraining, the participant completed the 6MWT [26] and TFTs [27] with the supervision and instruction of a licensed physical therapist with expertise in Pompe disease (LC). Volitional PCF (L/s) was measured during volitional cough using a calibrated oral pneumotachograph system (MLT1000L, ADInstruments; Colorado Springs, CO).

Table 1
Participant Demographic Information at Baseline for RMT #1 and RMT #2

	RMT 1	RMT 2
Age at pretest (month;year)	5 y; 9 m	6 y; 7 m
Ambulatory status	Primarily wheelchair dependent; Rifton Pacer Walker & AFOs for walking	Primarily wheelchair dependent; KidWalk walker & AFOs for walking
Baseline MIP (cm H_2O) (percent predicted)	21.8 (36%)	31.5 (39%)
Baseline MEP (cm H_2O) (percent predicted)	42.6 (60%)	71.1 (81%)
FVC (l) (percent predicted)	0.88 (81%)	0.94 (79%)
FEV1 (l) (percent predicted)	0.87 (88%)	0.92 (85%)
PEF (l/s) (percent predicted)	3.40 (148%)	2.36 (92%)
Enzyme replacement therapy (ERT) dose	20 mg/kg weekly	20 mg/kg weekly

AFO = ankle-foot orthotic, MIP = maximum inspiratory pressure, MEP = maximum expiratory pressure, cmH_2O =A centimeters water pressure, FVC = forced vital capacity, l = liters, FEV1 = forced expiratory volume in 1 second, PEF = peak expiratory flow, l/s = liters per second.

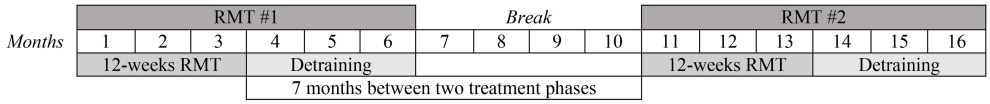

Fig. 1. Participation in two 12-week RMT regimens over 16 months. Seven months of detraining occurred between the 2 treatment phases. In each regimen, assessments occurred immediately prior to starting RMT (pretest), immediately following completion of 12-weeks RMT (posttest), and again after 3 months of RMT withdrawal (detraining).

2.3.3. Respiratory muscle training (RMT) therapy

Following identical procedures from RMT #1 [2], the participant participated in RMT therapy sessions with a licensed speech pathologist ("RMT Clinician", KC) every other week throughout the 12-week RMT regimen. RMT was individualized to provide progressive inspiratory and expiratory pressure-threshold resistance based upon the participant's inspiratory and expiratory strength. MIP and MEP were assessed at the beginning of each RMT therapy session, and both IMT and EMT were completed at 60–70% of MIP and MEP, respectively.

FDA-approved, commercially available, handheld inspiratory- and expiratory-type pressure-threshold RMT devices were used (Threshold PEP, Threshold IMT-Phillips Respironics, Andover, MA, USA; EMST 150-Aspire Products, Gainesville, FL, USA). The devices were calibrated to ensure accurate pressure-threshold resistance as previously described [1,2]. The participant completed IMT and EMT repetitions in sets of 25, performing a total of 75 repetitions of EMT and 75 repetitions of IMT per session while the RMT clinician trained her and her family for successful repetitions and monitored RMT tolerance. If accuracy was $<$ 90% within any set, pressure-threshold resistance was reduced to 60% of MIP or MEP for the next set of repetitions.

The home-based RMT program included 3 sets of 25 repetitions of both IMT and EMT 5 days per week, maintenance of a treatment log to document adherence and accuracy with RMT, and a directive to discontinue RMT and contact the PI if negative side effects emerged such as pain.

2.4. Data analysis

The magnitude of change from pretest to posttest, posttest to post-detraining, and pretest to post-detraining was determined for the primary outcome measures of MIP and MEP using Cohen's measure of effect size (d) as defined by Busk and Serlin's first equation for single-subject d [21]. Simply stated, d is obtained by subtracting the mean value of the first assessment from the mean of the second assessment, divided by the standard deviation of the first assessment. Conservative interpretation guidelines for effect size calculations were established in which $d < 0.6$ is negligible, $d \geqslant 0.6$ modest, $d \geqslant 1.0$ large, and $d \geqslant 2.0$ very large. Descriptive statistics are provided for the exploratory outcome measures and PCF.

3. Results

Participant demographic data at baseline for RMT #1 and #2 are provided in Table 1. In both 12-week RMT regimens, the participant was prescribed 9,000 total RMT repetitions (4,500 IMT and 4,500 EMT). During RMT #2, the participant reported completion of 4350 IMT repetitions and 4350 EMT repetitions for

Table 2
MIP values for RMT #1 and RMT #2

Maximum Inspiratory Pressure (MIP)	RMT 1[a]	RMT 2[b]
Pretest (cmH_2O)	21.8 (36% predicted)	31.5 (39% predicted)
Posttest (cmH_2O)	31.9 (53% predicted)	39.3 (49% predicted)
Postdetraining (cmH_2O)	33.5 (55% predicted)	36.8 (46% predicted)
Pretest to Posttest (12 weeks)		
Δ MIP (cmH_2O)	10.1	7.8
% change	46.3	24.8
Effect size (d)	2.40	2.92
Posttest to Postdetraining (3 months)		
Δ MIP (cmH_2O)	1.6	−2.5
% change	5.0	−6.4
Effect size (d)	0.92	−0.70
Pretest to Postdetraining (6 months)		
Δ MIP (cmH_2O)	11.7	5.3
% change	53.7	16.8
Effect size (d)	2.79	1.99
Cumulative Change for RMT #1 and RMT #2 (16 months)		
Δ MIP (cmH_2O)	15.0	
% change	68.8	
Effect size (d)	3.57	

cmH_2O = centimeters water pressure, d = Cohen's d effect size statistic, Δ = change. [a]reference value for child aged 4–6 years = 60.6 cmH_2O for MIP [30]. [b]reference value for child aged 7–9 years = 80.8 cmH_2O for MIP [30].

an overall total of 8700 RMT repetitions, representing self-reported adherence of 97% to the prescribed RMT program. On average, she completed her home therapy program approximately 5 days per week and both IMT and EMT were completed with a mean percent accuracy of 99% per self-report. Neither the participant nor her caregivers reported pain or other adverse side effects associated with RMT.

3.1. Primary dependent variables

As seen in Fig. 1, 7 months of detraining occurred from cessation of training at posttest during RMT #1 and initiation of training at pretest during RMT #2. During this time, MIP declined by 1% (from 31.9 to 31.5 cm H_2O) and MEP declined 9% (from 77.8 to 71.1 cm H_2O). Pretest values for RMT #2 remained elevated compared to pretest values for RMT #1. Pretest MIP for RMT #2 (31.5 cm H_2O) was 45% greater than pretest MIP for RMT #1 (21.8 cm H_2O), while pretest MEP for RMT #2 (71.1 cm H_2O) was 67% greater than pretest MEP for RMT #1 (42.6 cm H_2O).

3.1.1. Maximum inspiratory pressure

Based on gender and age [30], predicted MIP for the participant was 80.8 cm H_2O at the start of RMT #2. The participant's mean MIP was 31.5 cm H_2O (39% predicted) at pretest, 39.3 cm H_2O (49% predicted) at posttest, and 36.8 cm H_2O (46% predicted) at post-detraining. From pretest to posttest, MIP increased by 25% ($d = 2.92$). From posttest to post-detraining, MIP declined by 6% ($d = -0.70$). From pretest to post-detraining, MIP increased a total of 17% ($d = 1.99$) during RMT #2. Cumulatively, MIP increased by 15.0 cm H_2O over the entire 16 months, from 21.8 cm H_2O to 36.8 cm H_2O, an increase of 69% ($d = 1.99$). Changes in the participant's MIP during RMT #1 and RMT #2 are summarized in Table 2.

3.1.2. Maximum expiratory pressure

Based on gender and age [30], predicted MEP for the participant was 87.8 cm H_2O at the start of RMT #2. The participant's mean MEP was 71.1 cm H_2O (81% predicted) at pretest, 86.6 cm H_2O (99% predicted) at posttest, and 84.0 cm H_2O (96% predicted) at post-detraining. From pretest to posttest, MEP increased by 22% ($d = 2.65$). From posttest to post-detraining, MEP declined by 3% ($d = -0.36$). From pretest to post-detraining, MEP increased a total of 18% ($d = 2.21$) during RMT #2. Cumulatively, MEP increased by 41.4 cm H_2O over 16 months, from 42.6 cm H_2O to 84.0 H_2O, an increase of 97% ($d = 5.10$). Changes in the participant's MEP during RMT #1 and RMT #2 are summarized in Table 3.

3.2. Exploratory outcomes

Changes in the participant's 6MWT, TFTs, and PCF during RMT regimens #1 and #2 are summarized in Tables 4–6. Due to the participant's gross motor im-

Table 3
MEP values for RMT #1 and RMT #2

Maximum Expiratory Pressure (MEP)	RMT 1[a]	RMT 2[b]
Pretest (cmH_2O)	42.6 (60% predicted)	71.1 (81% predicted)
Posttest (cmH_2O)	77.8 (109% predicted)	86.6 (99% predicted)
Postdetraining (cmH_2O)	82.6 (116% predicted)	84.0 (96% predicted)
Pretest to Posttest (12 weeks)		
Δ MIP (cmH_2O)	35.2	15.5
% change	82.6	21.8
Effect size (d)	4.33	2.65
Posttest to Postdetraining (3 months)		
Δ MIP (cmH_2O)	4.8	−2.6
% change	6.2	−3.0
Effect size (d)	1.35	−0.36
Pretest to Postdetraining (6 months)		
Δ MIP (cmH_2O)	40.0	12.9
% change	94.0	18.1
Effect size (d)	4.93	2.21
Cumulative Change for RMT #1 and RMT #2 (16 months)		
Δ MEP (cmH_2O)	41.4	
% change	97.2	
Effect size (d)	5.10	

cmH_2O = centimeters water pressure, d = Cohen's d effect size statistic, Δ = change. [a]reference value for child aged 4–6 years = 71.5 cmH_2O for MEP [30]. [b]reference value for child aged 7–9 years = 87.8 cmH_2O for MEP [30].

Table 4
6MWT values for RMT #1 and RMT #2

6 Minute Walk Test (6MWT)	RMT 1	RMT 2
Pretest (m)	30.0	52.1
Posttest (m)	62.4	50.5
Postdetraining (m)	74.9	56.2
Pretest to Posttest (12 weeks)		
Δ 6MWT (m)	32.4	−1.6
% change	108.0	−3.1
Posttest to Postdetraining (3 months)		
Δ 6MWT (m)	12.5	5.7
% change	20.0	11.3
Pretest to Postdetraining (6 months)		
Δ 6MWT (m)	44.9	4.1
% change	149.7	7.9
Cumulative Change for RMT #1 and RMT #2 (16 months)		
Δ 6MWT (m)	26.2	
% change	87.3	

m = meters, d = Cohen's d effect size statistic, Δ = change.

Table 5
Time to walk 10 m for RMT #1 and RMT #2

Walk 10m (s)	RMT 1	RMT 2
Pretest (s)	112.0	17.5
Posttest (s)	38.2	16.5
Postdetraining (s)	35.4	16.1
Pretest to Posttest (12 weeks)		
Δ walk 10m (s)	−73.8	−1.0
% change	−65.9	−5.7
Posttest to Postdetraining (3 months)		
Δ walk 10m (s)	−2.8	−0.4
% change	−7.3	−2.4
Pretest to Postdetraining (6 months)		
Δ walk 10m (s)	−76.6	−1.37
% change	−68.4	−8.0
Cumulative Change for RMT #1 and RMT #2 (16 months)		
Δ walk 10m (s)	−95.9	
% change	−85.6	

m = meters, s = seconds, d = Cohen's d effect size statistic, Δ = change. *note (–) represents improvement in function.

pairments, she was unable to complete two of the TFTs included in the study protocol (supine to stand and climbing stairs).

3.2.1. Six minute walk test

Distance walked on the 6MWT in RMT #2 was 52.1 m at pretest, 50.5 m at posttest, and 56.2 m at post-detraining with use of a KidWalk walker and bilateral AFOs. From pretest to posttest, distance walked decreased by 3.1%. From posttest to post-detraining, distance walked increased by 11.3%. Overall, from pretest to post-detraining, distance walked increased by 7.9%. Cumulatively, distance walked on the 6MWT increased by 26.2 m, an improvement of 87.3% over 16 months. Changes in the participant's 6MWT during RMT #1 and RMT #2 are summarized in Table 4.

3.2.2. Time to walk 10 meters

Time to walk 10 meters in RMT #2 was 17.5 seconds (s) at pretest, 16.5 s at posttest, and 16.1 s at post-detraining with use of a KidWalk walker and bilateral AFOs. From pretest to posttest, time to walk 10 meters improved by 5.7%. From posttest to post-detraining, time to walk 10 meters improved by 2.4%. Overall, from pretest to post-detraining, time to walk 10 meters

Table 6
PCF values for RMT #1 and RMT #2

Peak Cough Flow (l/s) (PCF)	RMT 1	RMT 2
Pretest (l/s)	2.92	3.54
Posttest (l/s)	3.51	4.14
Postdetraining (l/s)	3.44	3.38
Pretest to Posttest (12 weeks)		
Δ PCF (l/s)	0.59	0.6
% change	20.2	16.9
Posttest to Postdetraining (3 months)		
Δ PCF (l/s)	−0.07	−0.76
% change	−2.0	−18.4
Pretest to Postdetraining (6 months)		
Δ PCF (l/s)	0.52	−0.16
% change	17.8	−4.50
Cumulative Change for RMT #1 and RMT #2 (16 months)		
ΔPCF (l/s)	0.46	
% change	15.8	

l/s = liters per second, d = Cohen's d effect size statistic, Δ = change.

improved by 8%. Cumulatively, time to walk 10 meters decreased by 95.9 s, an improvement of 85.6% over 16 months. Changes in the participant's time to walk 10 meters during RMT #1 and RMT #2 are summarized in Table 5.

3.2.3. Peak cough flow

PCF in RMT #2 was 3.54 L/s at pretest, 4.14 L/s at posttest, and 3.38 L/s at post-detraining. From pretest to posttest, PCF improved by 17%. From posttest to post-detraining, PCF declined by 18%. Overall, from pretest to post-detraining, PCF declined by 5%. Cumulatively, PCF increased by 0.46 L/s, an improvement of 16% over 16 months. Changes in the participant's PCF during RMT #1 and RMT #2 are summarized in Table 6.

4. Discussion

Although ERT prolongs ventilator-free survival [7, 8], some children demonstrate progressive respiratory muscle weakness [10,12–15]. Therefore, a simple, low-cost, largely home-based training program that can effect substantial changes in respiratory muscle strength in conjunction with ERT holds great appeal. Our results in a child with IOPD support our hypotheses that a second course of our intensive 12-week RMT regimen would result in additional increases in inspiratory and expiratory strength that were at least large in magnitude ($d \geqslant 1.00$) and that peak MIP and MEP values over this participant's entire participation would be achieved at posttest following the second course of RMT. Following the two RMT regimens, her MIP improved from 36% of predicted to 46% of predicted, and her MEP increased from 60% of predicted to 96% of predicted for gender and age. Both RMT #1 and RMT #2 were associated with very large effect sizes based on Cohen's d statistic. However, when comparing the results from RMT #2 to RMT #1, the response to training was less robust based on percent change of MIP and MEP.

Despite the progressive myopathy and respiratory muscle weakness associated with Pompe disease, even when treated with ERT, increases in respiratory strength associated with RMT appeared to be relatively persistent following withdrawal of training in this participant. Peak MIP and MEP values were noted at post-detraining assessment in RMT #1, indicating no evidence of detraining following 3 months of RMT withdrawal in the first experiment. As expected, MIP and MEP declined (by 1% and 9%, respectively) after 7 months of detraining between the two RMT regimens. However, this represents retention of 45% of the gains in MIP and 67% of the gains in MEP realized during RMT #1. In contrast to the first RMT regimen, small declines in MIP and MEP (6% and 3%, respectively) were observed after 3 months of RMT withdrawal in RMT #2, though effect sizes remained large for MIP and very large for MEP at post-detraining. These data suggest RMT may effect durable increases in respiratory muscle strength, even in the setting of progressive neuromuscular disease [31].

The accumulation of glycogen in skeletal muscle is known to cause weakness and hypotonia leading to delayed achievement of gross motor milestones and a unique set of persistent motor impairments in children with IOPD, despite treatment with ERT [4,6]. In addition to residual muscle weakness, reduced endurance as well as persistent gait and posture disturbances have been described [4]. Though skeletal muscle weakness is likely the largest contributing factor to chronic mobility impairments in IOPD, the cardiorespiratory system also plays a role in exercise endurance [32]. Therefore, the exploratory outcome measures included in the study protocol examined gross motor function before and after RMT.

Although improvements in this participant's performance on the 6MWT and time to walk 10 meters were noted during both 6-month experiments, their association with RMT-induced respiratory muscle strength increases is unclear. The expiratory muscles aid non-ventilatory motor function with contributions to trunk stability and mobility [33], representing a plausible mechanism by which RMT could impact motor per-

formance. Overall, the explanation for gross motor improvements is likely multifactorial, including increases in respiratory muscle strength, maturation, progress from ongoing physical therapy, modifications in assistive equipment used for mobility, and possibly participant effort.

Cough effectiveness has implications for airway protection, airway clearance, and overall pulmonary health. Voluntary PCF values < 270 L/min increase the risk for ineffective cough during respiratory illness and may necessitate use of airway clearance and secretion management techniques [34]. Reduced PCF is common in individuals with Pompe disease, and cough strength appears more severely compromised in children with IOPD than other disease phenotypes [35]. The physiological relationship between RMT-induced changes in respiratory strength and cough strength are perhaps more straightforward, given that a strong correlation between both inspiratory and expiratory muscle strength and PCF has been demonstrated in adults and children with Pompe disease [35] as well as other types of neuromuscular disease [36,37]. Our participant's results align with these findings, with increases in PCF from pretest to posttest evident in both experiments.

There are few additional data regarding RMT in children with Pompe disease. Smith and colleagues found little benefit from IMT in a group of 9 children with Pompe disease and chronic respiratory insufficiency [38]. However, 5 of the 9 participants in the study required full-time mechanical ventilation and thus demonstrated greater respiratory involvement at baseline than our participants.

We know of no studies that have investigated the benefits of additional RMT after a period of withdrawal. In fact, the effects of retraining or periodic training have not been studied in any form of exercise in individuals with neuromuscular disease. However, the exercise literature reports benefit from retraining with both aerobic and resistance-based exercise in healthy adults. Many studies report periodic detraining supports long-term muscle adaptation [39,40].

Alternative explanations for our findings must be considered. Considering that the participant was receiving ERT, one such explanation is that the observed respiratory strength increases were the result of drug treatment rather than RMT. However, this explanation appears unlikely due to the magnitude of respiratory strength increases observed with ERT when combined with RMT versus with ERT alone [41]. Another alternative explanation of our findings is the possibility that observed increases in MIP and MEP were due to learning effects. To control for learning effects, our study protocol was designed to obtain repeated measures of MIP and MEP during multiple test sessions, produced with minimal variability.

The limitations of this study include the case report of a single participant with lack of replication of retraining results in other participants. The effort-dependent nature of our primary dependent variables (MIP, MEP) and our exploratory outcome measures (6MWT, TFTs, PCF) is also a limitation; future research should explore the use of non-volitional measures of respiratory strength (electrical/magnetic phrenic nerve stimulation), as well as supplementary volitional measures (sniff nasal inspiratory pressure). An additional limitation is the use of self-reported adherence data; the results would be strengthened if the treatment dose (number of repetitions attempted, number of successful repetitions, and frequency of exercise) was quantified with objective measurements. Clearly, replication of the study protocol in additional children with IOPD is needed to establish safety, make preliminary estimates of treatment effect, and explore factors associated with treatment response, such as overall disease severity or baseline respiratory muscle involvement. The addition of a control condition would also strengthen future findings in this area.

In summary, RMT appears to be a promising adjunctive treatment for respiratory muscle weakness in children with IOPD, with cumulative benefit from retraining observed in one participant. Though much additional research is needed, this study suggests that children with Pompe disease may be able to safely participate in multiple intensive RMT regimens and demonstrate measurable increases in respiratory strength.

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Conflict of interest

LEC, PSK, and HNJ have received research/grant support and honoraria from Sanofi Genzyme Cor-

poration. 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. KDC and RMK have no conflicts of interest to report.

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