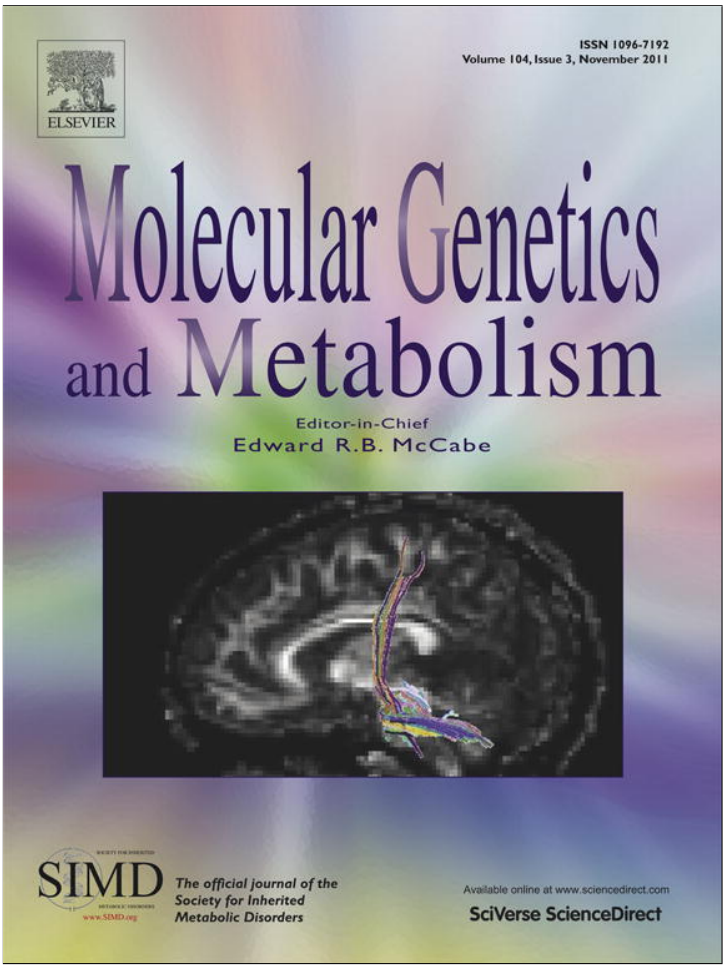

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Brief Communication

Increased inspiratory and expiratory muscle strength following respiratory muscle strength training (RMST) in two patients with late-onset Pompe disease

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ABSTRACT

Respiratory muscle strength training (RMST) is an exercise-based intervention which targets respiratory muscle weakness. We implemented RMST in two patients with late-onset Pompe disease (LOPD), both who had received long-term enzyme replacement therapy and had severe respiratory weakness. Over 16–32 weeks, inspiratory muscle strength increased by 73–74%. Expiratory muscle strength increased 31–48% over 12–22 weeks. These findings suggest that RMST may increase respiratory muscle strength, even in the setting of LOPD and severe baseline weakness.

Respiratory muscle weakness remains a therapeutic challenge which results in substantial morbidity and mortality in both the infantile and late-onset phenotypes of Pompe disease. In the late-onset form, respiratory weakness increases with disease progression resulting in decreased vital capacity, sleep disturbances, weak cough, respiratory insufficiency, and acute respiratory failure. In an untreated cohort of adults with Pompe, respiratory muscle weakness was present in 90% of subjects and expiratory muscle strength declined 7.3% over 1 year [1]. Both the inspiratory and expiratory muscles are inevitably affected, though it is not uncommon to encounter weakness isolated to either the inspiratory or expiratory muscles early in the disease. Over time, the decline of inspiratory and expiratory muscle strength becomes severe. Significantly, respiratory failure is the most common cause of death in adults with Pompe disease [2]. Recent data suggest that neural output to the diaphragm is also reduced, further complicating the nature of respiratory muscle involvement in this condition [3].

Enzyme replacement therapy (ERT) with alglucosidase alfa has altered the natural course of Pompe disease. In late-onset Pompe, ERT has been shown to benefit motor function and stabilize respiratory function over 18 months [4]. Despite such remarkable advances in clinical management and scientific understanding, respiratory weakness and associated morbidity and mortality remain a major therapeutic challenge in this condition.

Advancements in exercise physiology, strength training, and motor learning have led to improved understanding of the processes involved in strengthening the striated, spinally innervated, inspiratory and expiratory skeletal muscles. Modern respiratory muscle strengthening approaches are often termed respiratory muscle strength training (RMST). RMST is an exercise-based treatment which targets the inspiratory and expiratory muscles via handheld, pressure-threshold respiratory trainers individually calibrated to provide an appropriate inspiratory or expiratory resistance load. RMST has been used in healthy and disordered populations to strengthen the inspiratory muscles (i.e., inspiratory muscle strength training [IMST]), the expiratory muscles (i.e., expiratory muscle strength training [EMST]), or both (i.e., RMST).

A literature regarding the possible therapeutic effects of RMST in other forms of neuromuscular disease (NMD) has emerged. For example, McCool and Tzelepis reviewed seven studies which used IMST in 75 patients with various types of NMD (most with Duchene muscular dystrophy [DMD]) and concluded that: "investigators have generally shown that the inspiratory muscles are similar to other muscle groups in that they can be trained for…force …" [5, p. 1006]. Subsequent data support the possible positive influence of RMST to enhance respiratory muscle strength in NMD. For example, RMST was applied in 21 subjects with DMD or spinal muscular atrophy (SMA) and 20 controls [6]. The experimental group demonstrated significant improvements in inspiratory strength, expiratory strength, and dyspnea after 6 months of training. Similarly, Koessler and colleagues reported on the use of IMST for 24 months in 27 subjects with DMD or SMA [7]. Three severity groups were established based on baseline

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vital capacity and all severity groups demonstrated significant increases in inspiratory strength over 10 months of training.

Although a variety of RMST programs have been studied in diverse patient populations, we are unaware of any data on the use of RMST in Pompe disease. We describe the clinical use of RMST in two patients with late-onset disease and severe respiratory muscle weakness. Both continued their long-term course of ERT via biweekly infusions throughout RMST.

1. Material and methods

Patient 1 was a 55 year-old white male with symptoms of Pompe disease for over 30 years. Patient 2 was a 64 year-old white female who had been diagnosed with Pompe disease approximately 15 years prior. Both patients had received biweekly infusions of alglucosidase alfa for over 3 years upon initiation of RMST and this ERT regimen was maintained throughout, though patient 1's dosage was decreased briefly due to worldwide drug shortages at one point.

Maximum inspiratory and expiratory pressures (MIP and MEP, respectively) were obtained to determine respiratory strength. Both patients had severe respiratory muscle weakness: Patient 1 had a baseline MIP of 28 cm H_20 (27% predicted) and MEP of 61 cm H_20 (28% predicted), while patient 2 had a baseline MIP of 28 cm H_20 (39% predicted) and MEP was 37 cm H_20 (27% predicted) [8]. Baseline forced vital capacity (FVC) were obtained during routine clinical care. Patient 1 had a FVC of 2.25 L sitting upright and 1.18 L supine, 45% and 24% of predicted, respectively. Patient 2 had a baseline FVC of 1.19 L sitting (45% predicted) and 0.78 L supine (29% predicted).

Patient 1 and patient 2 each initiated RMST with IMST or EMST only in order to facilitate early success and promote compliance with an intensive home therapy program. Pressure-threshold respiratory trainers were calibrated to provide approximately 60% of MIP and MEP against inspiration (IMST) or expiration (EMST) based on each patient's current strength profile. Twenty-five repetitions of IMST or EMST only were completed twice daily, 6 days per week for 1 month to 10 weeks before RMST was entirely initiated. Patients were seen for clinic visits approximately every other week to monitor treatment response, measure MIP and MEP, and calibrate the respiratory trainer(s) to provide progressive resistance.

2. Results

Patient 1 completed 16 weeks of IMST and 12 weeks of EMST prior to being forced to withdraw from therapy due to an unrelated health event which resulted in surgery and an extended recovery. The RMST regimen of patient 2 was similar to that of patient 1, though RMST commenced with EMST only for 10 weeks before IMST was added. Patient 2 completed 32 weeks of EMST and 22 weeks of IMST.

As seen in (Fig. 1), patient 1 demonstrated progressive increases in inspiratory muscle strength over 16 weeks of IMST. MIP increased 74%, from 28 to 49 cm H_20. MEP also increased over 12 weeks of EMST, from 61 to 80 cm H_20, a strength increase of 31%. Percent predicted MIP increased

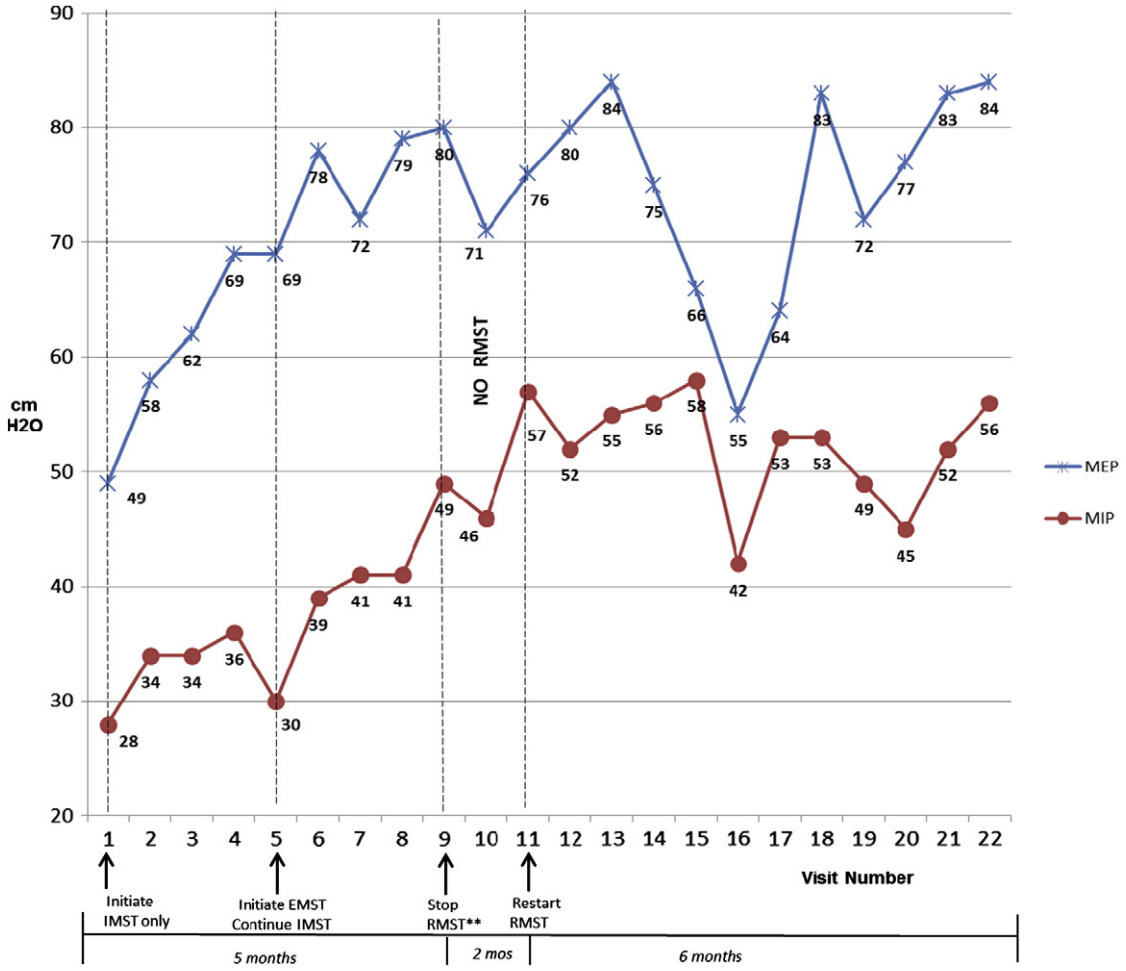

Fig. 1. Respiratory strength profile for patient 1 over approximately 13 months of respiratory muscle strength training (RMST). EMST = expiratory muscle strength training, IMST = inspiratory muscle strength training, MIP = maximum inspiratory pressure, MEP = maximum expiratory pressure, mos = months, **RMST discontinued due to an unrelated illness requiring surgery and post-operative recovery.

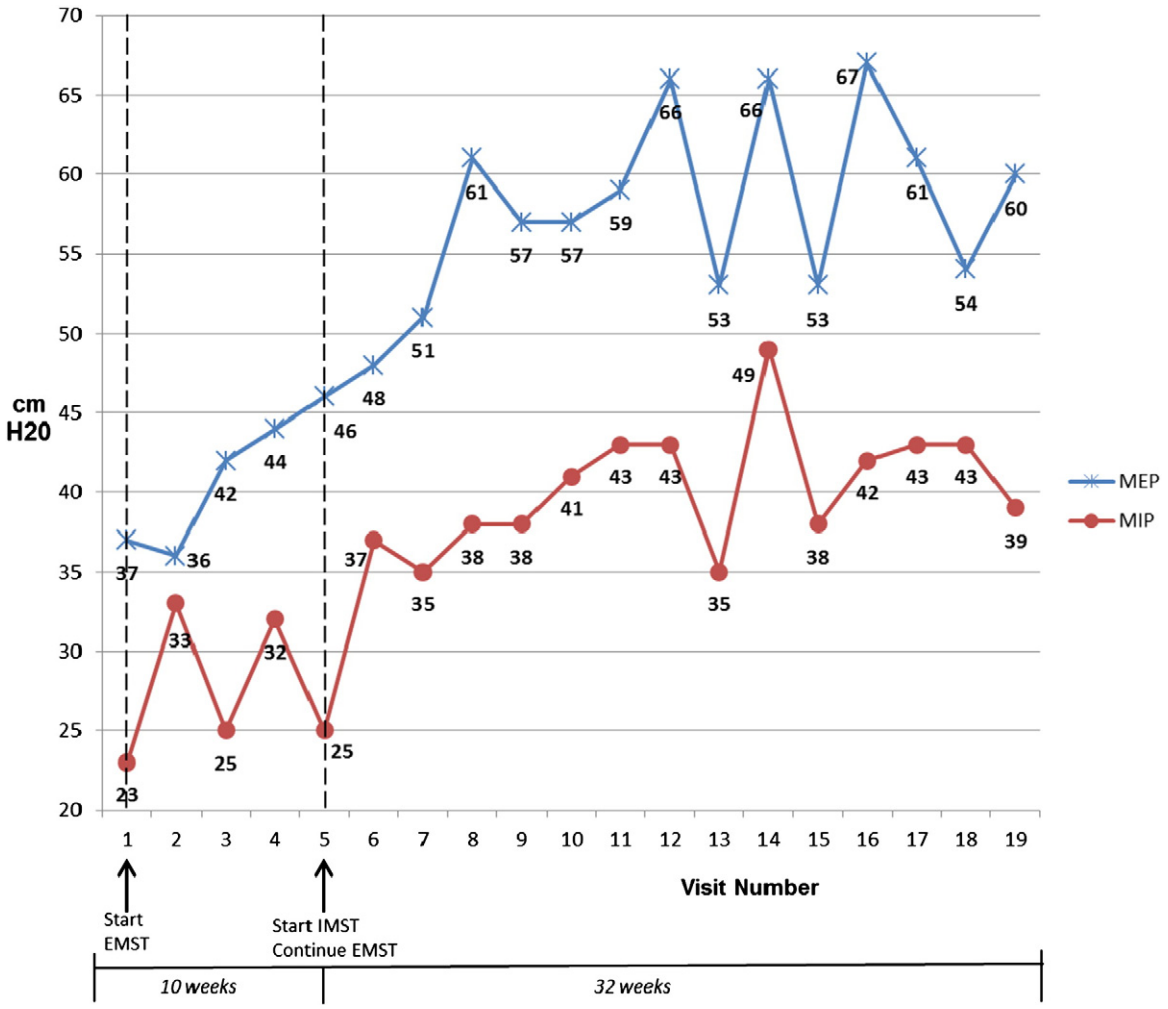

Fig. 2. Respiratory strength profile for patient 2 over 42 weeks of respiratory muscle strength training (RMST). EMST = expiratory muscle strength training, IMST = inspiratory muscle strength training, MIP = maximum inspiratory pressure, MEP = maximum expiratory pressure.

from 27 to 48% and percent predicted MEP increased from 28 to 37%. Due to the aforementioned medical illness, associated surgery, and recovery, an approximate 2 months withdrawal from RMST occurred. Following his return for RMST, MIP and MEP values were obtained at 57 cm H_20 and 76 cm H_20, respectively, which suggested persistent respiratory muscle strength enhancements. FVC was also obtained approximately 10 weeks after the discontinuation of RMST. FVC sitting was 2.50 L and supine was 0.98 L, 51% and 20% respectively of the predicted values. It was noted by the attending pulmonologist that FVC and functional status from a respiratory standpoint was stable. Continued improvements in MIP and MEP were observed following resumption of RMST.

Patient 2 also increased inspiratory and expiratory muscle strength during RMST in a progressive, systematic manner (see Fig. 2). Over 32 weeks of EMST, MEP increased 73% from 37 to 64 cm H_20. MIP increased 48% over 22 weeks of IMST, from 28 to 41 cm H_20. Percent predicted MIP increased from 36 to 53% and predicted MEP increased from 26 to 31%. FVC was also obtained after approximately 6 months of RMST. FVC sitting was 0.89 L and supine was 0.77 L, 34% and 29% of predicted, respectively. The attending pulmonologist noted that these values were stable with a slight decrease in sitting FVC in comparison to her previous exam.

3. Discussion

These preliminary data suggest that RMST may enhance respiratory muscle strength, even in patients with a progressive NMD such as LOPD and severe baseline weakness. Both patients demonstrated large increases in inspiratory and expiratory muscle strength with RMST. These strength enhancements appeared quickly in response to RMST and continued to increase in a predictable fashion over time without clear evidence of plateau. Both patients also endorsed functional benefits. For example, patient 1 reported that RMST facilitated his rapid ventilator wean when emergency surgery was required. Patient 2 reported an increased ability to participate in physical therapy and perform activities in her home.

Although both patients received ERT, this does not appear to explain the large increases in inspiratory and expiratory strength we observed. Previous data suggest that increases in MIP and MEP occur shortly after the initiation of ERT in LOPD, are smaller in magnitude, and plateau between 12 and 26 weeks. The magnitude of respiratory enhancements with ERT only in LOPD has been reported to be approximately 3–4% across subjects for both MIP and MEP [4].

Continued investigations into the therapeutic effects of RMST in Pompe disease and other forms of NMD are urgently needed and are in progress at our laboratory. RMST may emerge as a useful adjunctive treatment to ERT in Pompe disease, as well as other forms of NMD associated with respiratory weakness and resultant morbidity and mortality.

Acknowledgments

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