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ORIGINAL COMMUNICATION

Safety and efficacy of short- and long-term inspiratory muscle training in late-onset Pompe disease (LOPD): a pilot study

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Abstract

Background In patients with late-onset Pompe disease, progressive respiratory muscle weakness with predominantly diaphragmatic involvement is a frequent finding at later stages of the disease. Respiratory muscle training (RMT) is an established therapy option for patients with several neuromuscular disorders including Duchenne muscular dystrophy. Forced voluntary muscle contractions of inspiration and/or expiration muscles enhance ventilation by increasing respiratory coordination, endurance, and strength. Efficacy of RMT in LOPD is rarely examined, and the clinical studies performed are difficult to compare because of different training programs and protocols. This impedes a useful statement and recommendation about the safety and efficacy of respiratory muscle training.

Methods We conducted a monocentric unblinded single-arm pilot study in patients with LOPD to evaluate the safety and efficacy of inspiratory muscle training (IMT). The primary objective was to determine the efficacy of a 6-week repetitive IMT with a gradual increase of inspiratory resistance, measured by MIP (maximum inspiratory pressure) in the upright position. For statistical analysis, we used an A–B–C single subject design. The 6-week training-period A was followed by a 6-week non-training period B and an optional training period of 40 weeks in period C. The total study duration for the periods A, B and C was 52 weeks. Throughout the study, spirometry assessments (FCV, FEV1) and measurements of respiratory strength (MIP, MEP) were performed at defined time points, as well as capillary oximetry and capnometry, motor function test and patient's questionnaires for quality of life and dyspnea, measured by St. George's Respiratory Questionnaire (SGRQ) and MMRC-Dyspnea scale. For the cross-sectional comparison, a paired two-sided *t* test, and for the longitudinal comparison, a two-sample, two-sided *t* test were used. When data were not normally distributed, a Wilcoxon–Mann–Whitney test was added. Finally, the annual decline in FVC and FEV1 before and after IMT was compared.

Findings 11 subjects were included in this pilot study. Overall, IMT was well tolerated. In four subjects, a total of six adverse events related to the study procedures were noticed. Training compliance was excellent in the first weeks of training, but declined continuously in the extension period. There was a significant increase in our primary outcome measure MIP within the 6-week period of frequent IMT with a mean of 15.7% ($p=0.024$; $d=0.402$). A significant increase was also seen after week 52 by a mean of + 26.4% (mean + 13.4 cmH_2O, $p=0.001$, $d=0.636$). In the 6-week non-training interim-period (period B), the values remained stable, and there was no clinically meaningful decline in secondary outcome measures. The increase in MIP did not have any effect on secondary outcome measures like spirometry tests (FVC, FEV1), capillary blood gas analysis, motor function tests, patient's perceived quality of life or any significant change in dyspnea score.

Conclusions Frequent IMT improves MIP and thereby stabilizes and decelerates the decline of the diaphragm strength. The gradual increase of inspiratory resistance is well tolerated without any increase of side effects, as long as IMT is supervised and resistance is individually adjusted to the patient's perceived grade of exhaustion. Although we could not detect a significant impact on secondary outcome measures, IMT should be offered to all LOPD patients, especially to those who demonstrate a progressive decline in respiratory muscle function or are unable to receive ERT.

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Extended author information available on the last page of the article

Keywords Glycogen storage disease type 2 · Inspiratory muscle training (IMT) · Late-onset Pompe disease (LOPD) · Pompe disease · Respiratory weakness · Respiratory muscle training

Background

Pompe disease (glycogen storage disorder type II, OMIM 232300) is a rare, autosomal recessive multisystemic neuromuscular disorder. The estimated incidence varies among ethnicity and geography with 1 in 40,000 to 1 in 200,000 affected people globally [1, 2]. Up to date, more than 400 pathogenic mutations in the GAA gene are described, causing a variable degree of deficiency of the enzyme acid alpha-glucosidase (GAA) in lysosomes that degrades glycogen predominantly in skeletal muscle cells. The resulting accumulation of glycogen disrupts the architecture and function of affected cells and leads to a multisystem pathology and premature death [3, 4]. In late-onset Pompe disease (LOPD), a predominantly proximal muscle weakness becomes apparent at 30 years of age [5]. Orthopnea and/or exertional dyspnea occurs, and about one-third of patients will require noninvasive or invasive ventilation at later disease stages [6]. In some patients, respiratory failure may be the first symptom to be recognized [7–9]. In up to 70% of the patients, the progress of respiratory failure leads to premature death [9, 10]. Typically, inspiratory muscles are predominantly affected [7, 11]. Enzyme replacement therapy (ERT) with alglucosidase alfa has been approved in 2006 and is the only approved therapy to date [12]. In the absence of enzyme replacement therapy, a yearly decline of 3.2% in MIP and 2.3% in FVC is estimated [13, 14]. In clinical trials, a slowing in disease progression and a stabilization of pulmonary function were shown for patients receiving long-time ERT [15–19]. Depending on the study protocols for assessments of pulmonary function, forced vital capacity (FVC) in sitting and supine position, forced expiratory volume in the first second of the FVC maneuver (FEV1) and/or maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) are usually evaluated [20, 21]. However, despite ERT, long-term observational studies showed that up to about one-third of patients demonstrate suboptimal treatment response and have pulmonary decline leading to ventilator dependency [7, 13, 22].

Respiratory muscle training (RMT) is a well-known and established treatment in patients with chronic obstructive lung disease (COPD) [23], spinal cord injury and several neuromuscular disorders such as Duchenne muscular dystrophy [24–26]. Theoretically, inspiratory muscles are morphologically skeletal muscles and should respond to repeated training similar to any other locomotor muscle. The underlying mechanism of RMT is based on high-frequent repetitions of forced voluntary muscle contractions of inspiratory and/or expiratory muscles with an appropriate physiological load using pressure threshold devices [27–29]. The American Thoracic Society/European Respiratory Society (ATS/ERS) recommends inspiratory muscle training (IMT) in pulmonary rehabilitation guidelines in patients with suspected or confirmed respiratory muscle weakness [30]. So far, the number of published clinical studies of RMT in LOPD patients is low [22, 31, 32]. However, the existing studies of RMT in LOPD lack comparability because of different training programs and protocols. This impedes a useful recommendation about the safety and efficacy of respiratory muscle training in LOPD. Therefore, we performed a short- and long-term IMT pilot study in 11 LOPD patients.

In this pilot study, we prospectively evaluated the safety and efficacy of recurrent inspiratory muscle training (IMT) in patients with LOPD who were under enzyme replacement therapy (ERT). The primary objective was to determine the efficacy of a 6-week repetitive IMT with a gradual increase of inspiratory resistance, measured by MIP (maximum inspiratory pressure) in the upright position. The secondary objectives were changes on FVC, FEV1, MEP, capillary oximetry and capnometry, as well as functional muscular endurance (6MWT with Borg scale) and changes in quality of life, measured by St. George's Respiratory Questionnaire (SGRQ) and MMRC-Dyspnea scale. Additionally, after the short-term study of 6 weeks, we extended our evaluation of all assessments after the 6-week non-training period for another 40 weeks (total study period of 52 weeks).

Methods

Subjects and inclusion and exclusion criteria

The study was approved by the Ethics Committee of the Ludwig-Maximilians-University Munich, Germany (vote no. 689/16), and registered at the German Clinical Trials Register (DRKS) No. DRKS00014802. We recruited all subjects through our outpatient clinic and the German Pompe patient organization (Selbsthilfegruppe Glykogenose Deutschland e.V., http://www.glykogenose.de). Inclusion criteria were ≥ 18 years of age, confirmed LOPD by GAA gene mutations and patient's ability and willingness to perform regular inspiratory muscle training five times per week. Patients filled in a diary about their daily training success, performed repeated pulmonary lung function tests (PFT) and had capillary blood draws for blood gas analysis (pO_2, pCO_2). Exclusion criteria were continuous invasive ventilation, participation in other clinical studies using investigational

treatment and inability to have pulmonary lung function tests performed.

Study procedures and experimental design

We conducted a prospective monocentric unblinded single-arm pilot study in patients with LOPD to evaluate the safety and efficacy of regular inspiratory muscle training (IMT, Sect. "Respiratory muscle training"). For statistical analysis, we used an A–B–C single-subject design. The 6-week-training period A was followed by a 6-week non-training period B. If subjects had completed period A and B, they were asked to participate in the extension period for the following 40 weeks of inspiratory muscle training. The total study duration for all periods (A, B and C) was 52 weeks (Fig. 1; Fig. 7 supplements).

At baseline, medical history was taken and physical examination was performed for all subjects. Visits were performed every second week in period A and B, and every 8 weeks in period C. At each visit, adverse events were collected, and pulmonary function tests (PFT) as well as capillary blood gas analysis (cBGA) were obtained. The subjects were asked to fill out questionnaires about the impact of respiratory symptoms on their quality of life, using the St. George's Respiratory Questionnaire (SGRQ) and MMRC-Dyspnea scale. A 6-min-walk test, including Borg scale (Borg rating of perceived exertion, RPE) [33], was performed at baseline, at week 6 and week 12. For those subjects who continued the study in the extension period C, a 6-min walk test was performed at week 36 and week 52. All subjects were asked to fill out a study-specific diary about their performed IMT, containing the number of successful and unsuccessful training intervals and the maximum Borg scale of perceived exertion while training from 0 (no perceived exertion) to 10 (maximum perceived exertion). Except for the period B, the subject's diaries were reviewed, and the number of successful and unsuccessful IMT intervals was read out from the digital respiratory training device (Sect. "Respiratory muscle training" and Fig. 2). To evaluate the subject's adherence and motivation for the training, we did not give feedback or comment on the number of performed training intervals.

The pulmonary function tests (PFT) included forced vital capacity in sitting (FVC_{sit}) and supine position (FVC_{sup}) with the calculated percentage of predicted (%predicted) and drop of FVC, forced expiratory volume in the first second (FEV1), maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP). PFT assessments were obtained in accordance with the standards and recommendations of the statement of the American Thoracic Society and the European Respiratory Society [34]. The predicted reference values for FVC, FEV1, MIP and MEP were calculated according to the recommendations given in the "Guide to Spirometry", published by the German Airway League, the German Respiratory Society and the German Society of Occupational and Environmental Medicine [35]. We followed all the recommendations on the methodology of measurement, as elaborated in this guide. For spirometry, we used the KoKo PFT System© 2010 nSpire Health Inc. spirometer. MIP and MEP were measured in an upright

Week			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52
Visit No.	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Assessments:	Screening	Baseline	Training Period A			Non-Training Period B			Training Period C				
Inclusion/Exclusion	◆												
Clinical muscular status (MRC)		◆											
Patient reported outcome measures - St.-Georges Respiratory Questionnaire (SGRQ) - MMRC Dyspnea scale		◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Pulmonary function & respiratory muscle strength - FVC sitting and supine - FEV1 sitting and supine - Maximum inspiratory pressure - Maximum expiratory pressure	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
capillary blood gas analysis (O_2/CO_2)	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Six-minute-walk-test + Borg scale	◆					◆			◆		◆		◆
IMT: 7 intervals (1 Interval = 15 inhalations) per day on 5 days/week (=35 intervals / week = 525 inhalations)			◆	◆	◆				◆	◆	◆	◆	◆
Diary: daily performed number of IMT by patient			◆	◆	◆				◆	◆	◆	◆	◆
Check on completeness of the patient´s diary & review maximum perceived exertion (Borg)		◆	◆	◆	◆				◆	◆	◆	◆	◆
Assessment of adverse events / serious adverse events (AE/SAE)	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

Fig. 1 Study procedures. Study flowchart and study procedures during periods A, B and C. *IMT* inspiratory muscle training. *MRC* Medical Research Council score for assessing muscle weakness. *FVC* forced vital capacity. *FEV1* forced expiratory volume in the first second of the FVC maneuver

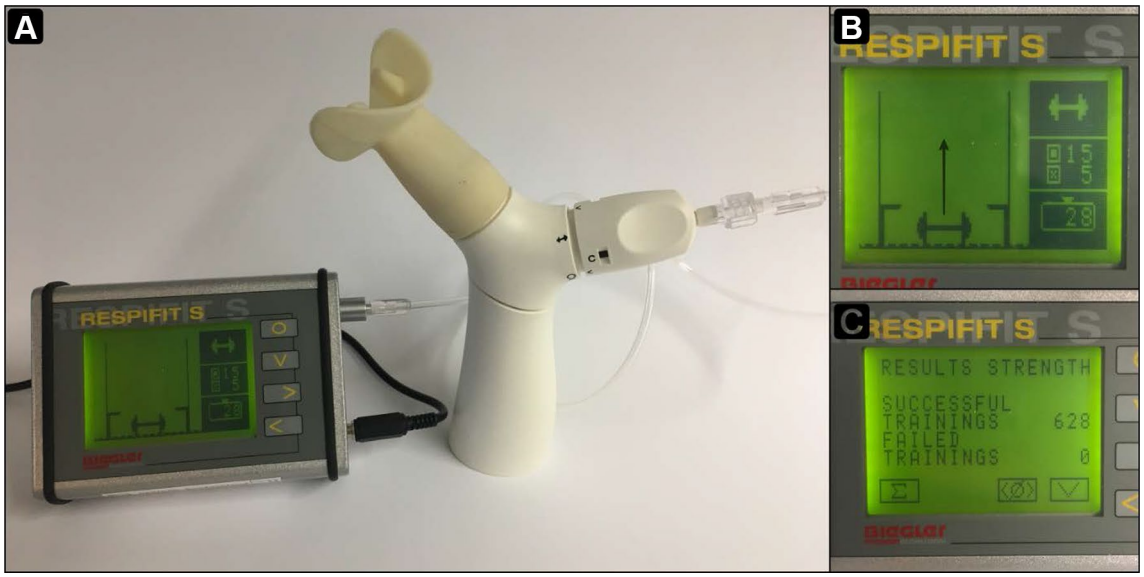

Fig. 2 Respiratory training device. An exemplary presentation of the respiratory training device RespifitS®: **a** Digital training device and patient´s module with a flanged rubber mouthpiece. **b** The graphic display provides feedback on the results of inspiratory muscle training. The patients have to breathe in deeply to lift the weight above the minimum load and hold it for at least 1 s. On the right, the display indicates the number of IMT to perform and the number of unsuccessful training intervals within one training interval. **c** Analysis view (accessible to the study team only) indicating the total number of performed successful and unsuccessful IMT

position with the microRPM™ CareFusion digital manometer, using a flanged rubber mouthpiece. For the respiratory muscle strength measurements MIP and MEP, at least four were performed, and the best three reproducible measurements were documented. For statistical analysis, the best effort was used.

Respiratory muscle training

The subjects performed an inspiratory muscle training (IMT), which is used to enhance ventilation by increasing respiratory coordination, endurance and strength. They performed a threshold resistance training, which is by far the most commonly used, researched and validated method of IMT [36]. We used the digital Respifit S®, a commercially available electronic respiratory training device. This device (a) allows to set up an individual resistance level with a range from 0 to 204 cmH_20, (b) provides a feedback for the patient about the number of successful and unsuccessful (insufficient) IMT via a small monitor (Fig. 2) and (c) allows to read out reports about successful and unsuccessful trainings to evaluate the training efficacy.

The subjects performed an inspiratory muscle training (IMT) on 5 days per week. The IMT consisted of seven intervals with 15 inhalations each (each about 2 min) and six breaks in between for about 1 min, depending on the subject's ability to perform the next inhalation. In total, we prescribed 105 inhalations per day and 525 inhalations per week, respectively. The total duration for IMT was about 30 min per day. If subjects failed to achieve the minimum inspiratory load, the inhalation was classified as "unsuccessful". If more than three unsuccessful inhalations occurred per interval, the whole interval was dropped and classified as unsuccessful training interval. The subjects documented the number of successful and unsuccessful IMT intervals in their diaries. The IMT started at period A with an inspiratory resistance of 30% of the subject's measured MIP at baseline. Every second week, inspiratory resistance was increased by 10%of baseline MIP, as long as the maximum Borg score was below seven within the last 2 weeks of training. Period A was followed by a 6-week non-training period (B). Subjects who had completed both periods A and B were asked to continue the IMT in the extension period (C) for the following 40 weeks. In this period C, the level of resistance was optionally increased by 10–15% of baseline MIP at every visit, depending on the subject's ability and willingness.

All subjects were asked to fill out a study-specific diary about their daily inspiratory muscle training, containing the number of successful and unsuccessful training intervals and the maximum Borg scale of perceived exertion while training from 0 (no perceived exertion) to 10 (maximum perceived exertion). At every visit, stored data about successful and unsuccessful training intervals were read out from the digital training device. We did not inform the subjects about the total number of stored successful and unsuccessful IMT intervals.

Safety and efficacy end points

For safety, a deterioration of > 15% of FVC in comparison with baseline measurement was defined as an adverse event (AE), as well as developing unusual symptoms such as myalgia of respiratory muscles while training or after training. Adverse events were collected from enrollment until the end of the study or participation plus 7 days and categorized by severity, seriousness and relationship to respiratory muscle training. All reported adverse events were classified according to the System Organ Class (SOC) adverse event terminology.

For efficacy, we collected measurements at each study time point in spirometry, MIP and MEP as well as capillary blood gas analysis and 6-min-walk test with Borg scale. Our predefined primary outcome parameter was an increase in MIP. For statistical analysis, we defined measurement points for every visit and compared the results at different time points (analysis Table 6 in supplements).

Statistical data analysis

For statistical analysis, we used R Software (V3.5.1, © The R Foundation). We calculated descriptive statistics where applicable. For the cross-sectional comparison, we used a paired two-sided *t* test. In the cases of non-normal distribution, we used a log transformation of the data. We compared the difference in the outcomes measured at baseline and after 6 weeks of training, as well as the difference in the outcomes at the beginning of the detraining period (last day of training), at the end of the detraining period and at the end of the extension period. For each visit, we defined a measurement point (M_1, M_2, etc.) and compared M_4 to M_1, M_7 to M_4, M_{12} to M_7 and M_{12} to M_1 (analysis Table 6 in supplements). Furthermore, we calculated the effect size (*d*) of the change, based on the measurements at the end of the period of training, non-training-period and extension period. Cohen's *d* is calculated as the difference in means of the measurements, divided by the pooled standard deviation.

To test the reliability of the cross-sectional analysis, we performed a longitudinal comparison. For this, we used a two-sample, two-sided *t* test, due to missing values. When the data were not normally distributed, we used a Wilcoxon–Mann–Whitney test. In the presence of ties in the variables' vector, we added a small amount of noise to the data, to meet the assumptions of the test. We compared the change in the outcomes over time in the periods A, B and C. We defined D_A as a union of all the changes in the measurements during the training period A, as well as D_B for period B and D_C for the extended training period C. For longitudinal comparison, we compared D_A to D_B, and D_B to D_C (analysis Table 6 in supplements).

To analyze whether RMT could prevent a decline in FVC and FEV1, we obtained historical data on FVC and FEV1 over the years from nine subjects, as far as data were available. Of these, seven subjects had data on FVC and FEV1 at the end of period C (52 weeks after onset of IMT). For analysis, we calculated the average annual decline in FVC and FEV1 in comparison to the change after 1 year of IMT, using a paired *t* test.

Because of the small sample size, we did not add an analysis of subgroups, correlation or regression.

Results

Patient population and demographic data

Between December 2016 and January 2017, we enrolled 11 subjects (9 women, 2 men) in the study (supplements Fig. 7). Three other patients did not provide informed consent at screening due to the high frequency of clinical appointments and assessments. All 11 subjects that were enrolled gave written informed consent prior to any investigational procedure and were ≥ 18 years of age. According to the clinical records, LOPD was confirmed by DNA mutation analysis of GAA genes in all patients. The common c.-45T > G mutation in the GAA gene was documented in 82% of patients. The mean age of the patients was 50 years (SD 15.6) at baseline. The mean age at onset of symptoms was 29.6 years (SD 11.4) and mean age at diagnosis was 38.82 years (SD 14.2). All patients received the standard dose of alglucosidase alfa enzyme replacement therapy every other week for a mean duration of 7.1 years (SD 3.0). At baseline, the subjects presented with a mild to moderate LOPD phenotype (mean MRC sum score 44.55; SD 2.81). One patient used a wheelchair part-time, and ten patients were fully ambulatory. Two patients were on noninvasive ventilation during the night. In nine patients, historical and baseline data revealed a restrictive pattern in FVC below 75% of predicted and a diaphragmatic involvement with a postural drop of ≥ 20% in eight patients. One patient was not able to perform spirometry test in supine position due to orthopnea. This patient was on nocturnal noninvasive ventilation since 10 years. The median BMI was 23.7 (SD 6.32). The demographic data of the study cohort at baseline are provided in Table 1 and supplements Table 7.

In the study periods A and B, all 11 patients performed all assessments. At the end of week 12, one female did not consent for the extension study (period C) due to a lack of motivation. Ten patients (8 women, 2 men) continued the training in the extension period (period C). One female withdrew her participation at week 36 due to a serious adverse event. Another female was lost to follow-up at week 52.

Table 1 Subject´s demographic data

	Male	Female	Total
n	2	9	11
Age; median (± SD)	56.00 (± 12.72)	54.00 (± 16.52)	54.00 (± 15.59)
Age onset of symptoms; median (± SD)	40.50 (± 9.19)	30.00 (± 10.68)	33.00 (± 11.36)
Age of diagnosis; median (± SD)	47.5 (± 9.19)	42.00 (± 14.83)	42.00 (± 14.24)
Duration of ERT; median (± SD)	7.50 (± 3.54)	7.00 (± 3.12)	7.00 (± 3.02)
Ventilator support (NIV, noninvasive ventilation); *n*	1	1	2

Subject´s demographic data. Age at onset of symptoms, age at baseline, age at diagnosis and age at start of enzyme replacement therapy (ERT) in years

A detailed version is presented in the supplementary section

NIV noninvasive ventilation. *SD* standard deviation

Eight patients (6 women) completed the whole study (supplements Fig. 7).

Safety

Overall, IMT was well tolerated. In total, seven adverse events occurred. There was one serious adverse event in one patient, in whom a left cerebral stroke in the Broca's speech area occurred at week 36. This subject discontinued from study participation (withdrawal). The preexisting cerebral angiopathy documented in the patient's records was considered as causative for this stroke, therefore we classified this SAE as non-related to the study intervention. Six adverse events occurred in four patients. Two upper respiratory tract infections in two patients were classified as moderate and not related to the study intervention. Myalgia of face muscles and lower back muscles was documented in three patients within the first training weeks. They were classified as mild to moderate and related to the study intervention. All patients continued the training per protocol, and myalgia resolved after some weeks of training in all subjects. One patient suffered from a headache after the training for the duration of 30–60 min in the first 2 weeks of training. The patient chewed on the flanged rubber mouthpiece while training in order not to hold the patient's module with his hands. After additional coaching by the study team, the headache resolved. We classified this AE as moderate and related to the study procedures. There was no association between the occurrence of adverse events and the increase of resistance, training period or Borg scale. All adverse events are listed in Table 2.

Table 2 Adverse events and serious adverse events

Description of adverse event	Severity of adverse event	Number of patients, *n* =	Relation to IMT	Treatment period, IMT resistance, max. Borg scale	Outcome
Myalgia of face muscles	Mild, AE	2	Related	1: period A, IMT 30%, max Borg 2 1: period A, IMT 40%, max Borg 3	Resolved
Myalgia of back muscles	Moderate, AE	1	Related	Period A, IMT 40%, max Borg 3	Resolved
Upper respiratory tract infection	Moderate, AE	2	Not related	1: period A, IMT 40%, max Borg 2 2: period B, no IMT, no Borg	Resolved
Headache	Moderate, AE	1	Possibly Related	Period A, IMT 60%, max Borg 3	Resolved
Stroke	Severe, SAE	1	Not related	Period C, IMT 60%, max. Borg 3	Partially resolved, discontinued study participation at week 36

IMT inspiratory muscle training, *AE* adverse event, *SAE* serious adverse event

Description, severity, classification and outcome of the reported adverse events and serious adverse events. Events were classified according to System Organ Class (SOC) adverse event terminology

Outcome measures and efficacy

Our primary outcome MIP showed a statistically significant increase after 6 weeks of IMT ($p=0.024$). Nine subjects showed an increase of MIP (82%). Three of them achieved a large increase of ≥ 15 cmH_2O. The mean increase after 6 weeks of training was + 7.6 cmH_2O (+ 15.7%) with a moderate effect size in cross-sectional analysis ($d=0.402$). One patient showed a decline of − 8 cmH_2O (-14%), and a second one remained stable (− 1 cmH_2O). In one patient, we assume that MIP artificially deteriorated due to fatigue, because both FVC and FEV1 improved. Especially for the two patients who were on noninvasive ventilation during nighttime, both showed an increase in MIP at week 6 and week 52 (+ 6%/+15% at week 6 and + 31%/+67% at week 52). After the non-training period (B), MIP decreased non-significantly on an average of − 2.27% ($p=0.770$). Confirmed with the longitudinal analysis, MIP was the only outcome with a statistically significant change in the training period (increase), compared to the detraining period (decrease) with $p=0.032$. Because of missing data from three subjects (withdrawal, dropout and lost to follow up), eight patients were analyzed for the full study period of 52 weeks. In these eight patients, MIP increased by a mean of + 13.4 cmH_2O (+ 26.4%), which was statistically significant and with a moderate to large effect size ($p=0.001$, $d=0.636$). Overall, the patients achieved a significant improvement in MIP both after the short-term IMT of 6 weeks and after the extended IMT of 40 weeks (Fig. 3).

Regarding statistically significant changes in secondary outcomes, MEP increased during the non-training period by 7.18 cmH_2O ($p=0.019$; $d=0.150$) and capillary pO_2 decreased by 5.82 mmHg ($p=0.037$; $d=0.115$). Both outcomes were associated with a negligible effect size ($d<0.2$).

For all other secondary outcome measurements, there were no statistically significant differences after training, after the non-training period, and in the comparison between baseline to week 52: FVC_{sit}, FVC_{sup}, drop of FVC, FEV1, capillary capnometry, 6-min-walk test including Borg scale and self-reported outcome measures (SGRQ and MMRC-Dyspnea scale) (supplements Table 4).

The comparison of the historical data on the annual change of FVC and FEV1 to the change after 1 year of IMT did not show a statistically significant difference in the decline of FVC ($p=0.625$) or in the decline of FEV1 ($p=0.326$) (Fig. 4a, b; supplements table 10).

Descriptive statistics for all variables measured are provided in detail in the supplementary material section.

Inspiratory muscle training and compliance

In period A, inspiratory resistance started at 30% of individual MIP at baseline and increased by 10% every second week in all subjects. The mean Borg score for the perceived exertion while training was between 1.3 and 1.8, and the maximum Borg score was 5. In period C, inspiratory resistance was individually increased by 10–15% at every visit, depending on the willingness, ability and motivation of the subjects. Only one subject was willing to increase his inspiratory resistance level up to 100% without any side effect. The mean inspiratory resistance was around 70% in the extension period; the mean Borg score was between 1.3 and 1.8, and the maximum Borg score was 5 (Fig. 5). Overall, the increase of inspiratory resistance was very well tolerated in both periods A and C. No subject has asked to reduce the level of resistance due to perceived exhaustion.

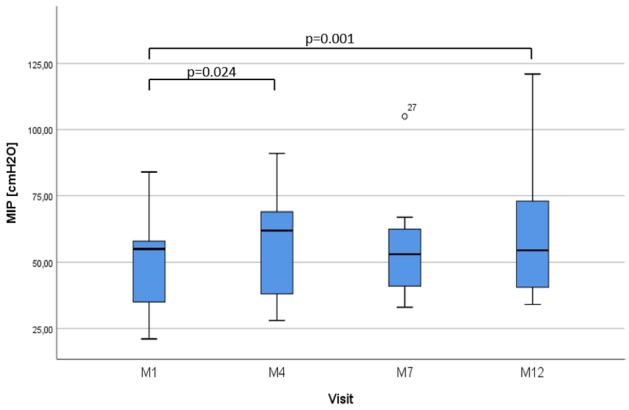

Fig. 3 Primary outcome measure: maximum inspiratory pressure (MIP). Box plots for measurement points M_1 (baseline), M_4 (after 6 weeks of training), M_7 (after 6 weeks of non-training) and M_{12} (at week 52, after 40 weeks of training). We found a statistically significant difference in our primary outcome measure MIP between baseline and after 6 weeks of IMT (M_1–M_4; $p=0.024$) as well as between baseline and week 52 (M_1–M_{12}; $p=0.001$). Because of missing data from three subjects, eight patients were analyzed during the extension period

In period A, adherence to training was excellent. The documented number of training intervals in the subject's diary was above the target of the minimum of prescribed training intervals in the first 6 weeks of training (107%). In contrast, during the extension period (period C), there was an increasing discrepancy between the target of IMT intervals and the number of training intervals that were documented by the subjects in their diaries (91%). Combining periods A and C, the number of performed IMT intervals was below the minimum number of required IMT intervals (94%) (Fig. 6; Table 3).

For an objective evaluation of successfully performed IMT, we read out the stored data from the training device at every visit. For the whole study, data were not available to readout or corrupt in 45%. For period A, the readout rate was 73%. Despite the missing data, 2314 IMT intervals were obtained in total, which was above the target of at least 2310 IMT intervals (100%)—yet an unknown number would have

Table 3 Number of IMT performed, stored in IMT training device and documented in the subject´s diary at different time points

Measurement point	M_2	M_3	M_4	M_8	M_9	M_{10}	M_{11}	M_{12}	Total	Total	Total
Week	Week 2	Week 4	Week 6	Week 20	Week 28	Week 36	Week 44	Week 52	Period A	Period C	IMT intervals
No. of subjects	11	11	11	10	10	10	9	8	–	–	–
Target IMT intervals	770	770	770	2800	2800	2800	2520	2240	**2310**	**13,160**	**15,470**
IMT device readout rate	43%	90%	78%	33%	33%	33%	50%	40%	**73%**	**38%**	**55%**
Training device: total no. of trainings	510	798	1006	1878	1830	1492	1608	2367	**2314**	**9175**	**11,489**
Training device: successful IMT intervals	510	785	991	1862	1821	1492	1595	2350	**2286**	**9120**	**11,406**
Training device: unsuccessful IMT intervals	–	13	15	16	9	–	13	17	**28**	**55**	**83**
Diary—IMT intervals total	847	847	828	2744	2413	2251	2140	2401	**2522**	**11,949**	**14,471**
Diary—IMT intervals successful	841	842	826	2731	2405	2248	2130	2377	**2509**	**11,891**	**14,400**
Diary—IMT intervals unsuccessful	6	5	2	13	8	3	10	24	**13**	**58**	**71**
Target/diary	71 (109%)	72 (109%)	56 (107%)	− 69 (98%)	− 395 (86%)	− 552 (80%)	− 390 (85%)	137 (106%)	**212 (109%)**	**− 1211 (91%)**	**− 999 (94%)**
Target/device	− 260 (66%)	28 (104%)	236 (131%)	− 922 (67%)	− 970 (65%)	− 1308 (53%)	− 912 (64%)	127 (106%)	**4 (100%)**	**− 3985 (70%)**	**− 3981 (74%)**

Mean values of the performed number of IMT as documented in the patient´s diary and stored in the digital training device. The minimum target number of IMT was seven training intervals per day with 15 repetitions on 5 days per week

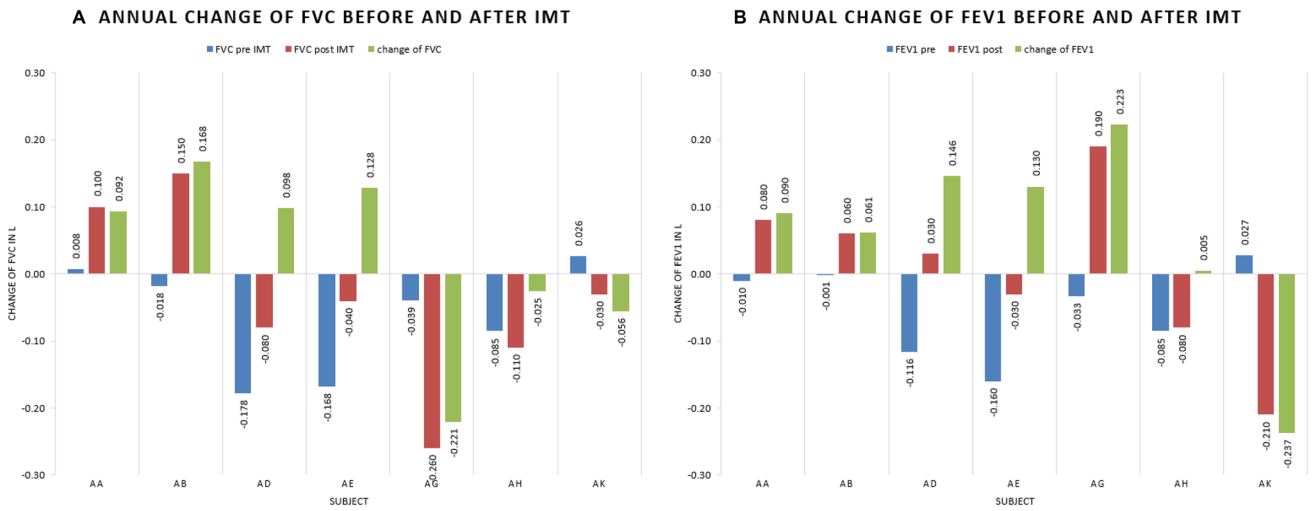

Fig. 4 Comparison of the annual decline in **a** FVC and **b** FEV1 before IMT and after IMT. We obtained data for seven LOPD patients on both the average change per year using historical data and on the change after week 52. Although non-significant, four patients showed an improvement in the decline in FVC after 1 year of training. Regarding FEV1, six subjects had an annual decline of FEV1 prior to IMT. After IMT, FEV1 improved in five subjects

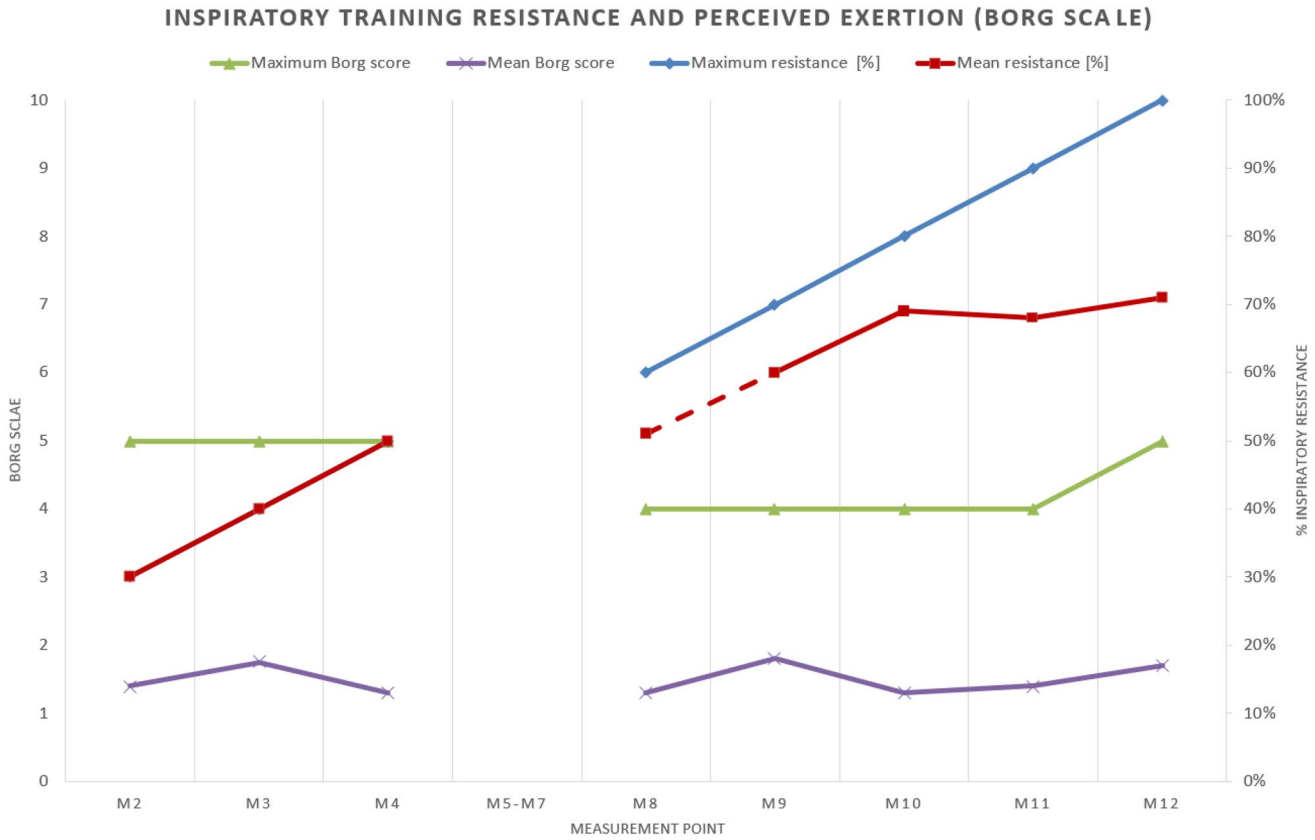

Fig. 5 Training resistance and perceived exertion, measured by the Borg scale. In period A (M_2–M_4), inspiratory resistance started at 30% of individual MIP at baseline and increased by 10% every second week in all subjects. The mean Borg score for the perceived exertion while training was between 1.3 and 1.8, and the maximum Borg score was 5. In period C (M_8–M_{12}), inspiratory resistance was individually increased by 10–15% at every visit, as requested by the subjects. Only one subject was willing to increase his inspiratory resistance up to 100%. Mean inspiratory resistance was around 70% in the extension period; the mean Borg score was between 1.3 and 1.8, and the maximum Borg score was 5

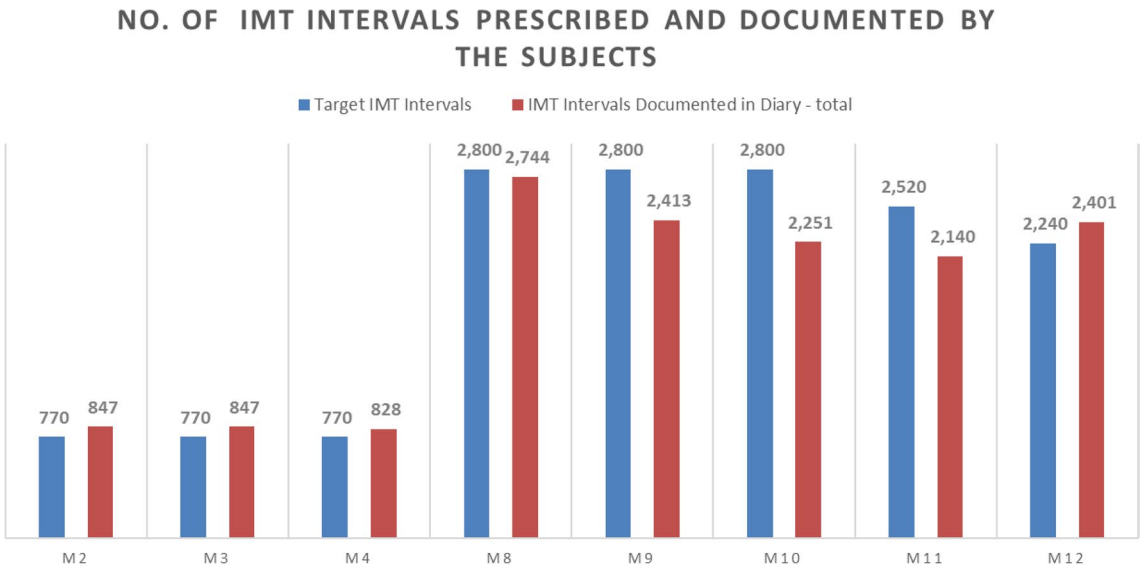

Fig. 6 The number of IMT prescribed and documented by the subjects in their diary. Subject´s adherence to the IMT: in period A (M_2–M_4), the documented number of training intervals in the subject´s diary was above the target of the minimum of prescribed training intervals. In period C (M_8–M_{12}), there was an increasing discrepancy between the target of the minimum of IMT intervals and the number of successful training intervals, documented by the subjects in their diaries. Because of too many missing data, we did not include an analysis of the number of successfully performed IMT intervals stored in the training device. A detailed summary of IMT intervals performed and stored in the training device is provided in Table 4 in the supplements

to be added from the missing data in 27%. For period C, a high amount of stored training data was corrupt, and the readout rate was meager at 38%. Because of this high rate of missing data, we did not include an analysis of the subject's adherence to IMT for period C that is based on the readouts from the IMT devices (Table 5).

Throughout the study, the rate of unsuccessful IMT was very low both in period A and period C, documented in the diaries as well as stored in the IMT device (0.5% in diary, 0.7% in IMT device) (Fig. 6; Table 3).

Discussion

The assessments of our prospective pilot study showed that there was a significant increase in our primary outcome measure MIP after a short period frequent IMT for 6 weeks with a mean of 15.7% ($p=0.024$; $d=0.402$). This increase in MIP did not have any effect on spirometry values, motor function tests or the patient's self-reported outcomes (SGRQ, MMRC-Dyspnea scale). We also included capillary blood gas analysis to detect changes in pCO_2 and pO_2 after training, both with negligible changes. In the following 6-week non-training period, MIP had no significant decline. It is likely that there was a long-term effect of IMT, which contributed to the lack of the decline in MIP during the period of no training. When analyzing the effects of IMT only for the extension period (period C), the most substantial difference between week 12 and week 52 was MIP with a mean change of 11.8%, which was not significant ($p=0.107$). When comparing measurements at baseline and week 52, there was a statistically significant increase in MIP with a mean of 26.4% ($p=0.001$, $d=0.636$). However, because of missing data from three subjects, this result should be interpreted with care. The loss of follow-up of these three patients might contribute to an overestimation of the effect, whereas the lack of training during period B for 6 weeks might contribute to an underestimation of the effect of IMT on MIP, as compared from baseline to week 52.

For all the secondary outcome measures, there was no clinically meaningful change comparing all the different measurement points.

The comparison of the historical average annual decline of FVC and FEV1 to those 1 year after training did not reveal a statistically significant difference in FVC ($p=0.625$) or FEV1 ($p=0.326$). Due to the small sample size, the p values were unreliable. Due to the retrospective nature of the historical data on FVC and FEV1, we cannot claim that all historical measurements of FVC and FEV1 were assessed consistently with the methodology used for spirometry in the prospective IMT study. This might have contributed to measurement errors and could have biased the results.

Training adherence was excellent in the first period of training. In contrast, in the extension period, the number of performed IMT decreased steadily, except for the weeks before the end of the study. We do not believe that

Table 4 Cross-sectional analysis of forced vital capacity (FVC), expiratory volume in the first second (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and capillary blood gas analysis, including oximetry and capnometry

	Capillary oximetry (mmHg)						Capillary capnometry (mmHg)					
	Median	Mean	sd	NAs	*p* value	*d*	Median	Mean	sd	NAs	*p* value	*d*
M1 (baseline)	82.20	82.87	17.73	0	–	–	39.00	40.88	5.82	0	–	–
M4 (training)	79.30	79.95	5.57	0	0.522		40.40	40.38	4.37	0	0.657	
M7 (detraining)	70.80	74.13	11.41	0	0.037	0.115	41.40	40.59	4.14	0	0.835	–
M12 (extension)	80.00	78.67	6.00	4	0.068	–	41.40	40.67	3.67	4	0.092	
M1 (baseline)	82.20	82.87	17.73	0	–	–	39.00	40.88	5.82	0	–	–
M12 (extension)	80.00	78.67	6.00	4	0.202		41.40	40.67	3.67	4	0.162	
	FVC (l)						FEV1 (l)					
	Median	Mean	sd	NAs	*p* value	*d*	Median	Mean	sd	NAs	*p* value	*d*
M1 (baseline)	2.18	2.37	0.59	0	–	–	1.98	2.00	0.49	0	–	–
M4 (training)	2.26	2.40	0.63	0	0.553		1.88	1.98	0.60	0	0.760	
M7 (detraining)	2.10	2.27	0.64	0	0.205	–	1.79	1.92	0.51	0	0.558	–
M12 (extension)	2.11	2.26	0.6	3	0.836		1.95	1.984	0.51	3	0.551	
M1 (baseline)	2.18	2.37	0.59	0	–	–	1.98	2.00	0.49	0	–	–
M12 (extension)	2.11	2.26	0.6	3	0.273		1.95	1.984	0.51	3	0.849	
	MIP (cmH_2O)						MEP (cmH_2O)					
	Median	Mean	sd	NAs	*p* value	*d*	Median	Mean	sd	NAs	*p* value	*d*
M1 (baseline)	55.00	48.55	18.02	0	–	–	64.00	72.73	29.43	0	–	–
M4 (training)	62.00	56.18	19.94	0	0.024	0.402	71.00	76.18	27.41	0	0.250	
M7 (detraining)	53.00	54.91	20.15	0	0.770	–	82.00	83.36	24.48	0	0.024	0.150
M12 (extension)	54.50	61.38	28.67	3	0.107		75.00	81.88	28.75	3	0.085	–
M1 (baseline)	55.00	48.55	18.02	0	–	–	64.00	72.73	29.43	0	–	–
M12 (extension)	54.50	61.38	28.67	3	0.001	0.636	75.00	81.88	28.75	3	0.075	

The *p* values are provided for comparisons of M_4 to M_1, M_7 to M_4, M_{12} to M_7, and M_{12} to M_1. Cohen´s *d* is only provided for *p* values < 0.005

the decreasing number of performed IMT correlates with increasing levels of resistance because the documented grade of exertion by Borg score did not exceed the score of 5 in any patient. It seems to be more likely that a lack of motivation is causative for a steadily decreasing number of performed IMT in this long-term period. In our opinion, these results correspond to some already published data on patients with COPD and their adherence to long-term respiratory muscle training [37, 38]. During the study, we did not motivate or give any feedback to the subjects on the numbers of successful performed IMT stored in the device, because we wanted to evaluate the patient's compliance to this method of training that—in our view—should be self-motivated, similar to physical activity and physiotherapy. However, considering our results, health-care professionals should pay more attention to the patients and try to motivate them continuously to avoid declining motivation and adherence.

Taking into account the results of previous studies on respiratory muscle training in patients with LOPD, we found equal outcome measures in our study cohort. In 2015, Harrison Jones et al. showed that there was a significant increase of MIP and MEP in eight patients in a 12-week training period [39]. Both outcome measures remained stable in a subsequent 12-week detraining period. The training regimen consisted of three sets of 25 repetitions of IMT and EMT on 5 days per week. Inspiratory and expiratory pressure threshold resistance was individually set, based on each subject's individual level of inspiratory and expiratory strength up to 60–70% of MIP and MEP, respectively. Every second week, supervised training was offered. In this trial, MIP increased in all eight subjects with a high degree in four patients by a mean of + 19.6%. MEP increased in seven out of eight patients significantly by a mean of 16.1% [39]. Compared to our study, after a 6 weeks training period, the mean increase of MIP was + 15.7% (7.6 cmH_2O), but the number of IMT repetitions with 525 per week was far below the prescribed number of training intervals in the study of Harrison Jones et al., who prescribed 750 IMT repetitions of IMT and EMT per week. The reasons for the better efficacy in this training set may be the higher number of training intervals, combined inspiratory and expiratory training and a higher resistance level at the beginning of the exercise. In a short-term study

Table 5 Longitudinal analysis

No. of subjects	Oximetry					Capnometry				
	Median	Mean	sd	NAs	*p* value	Median	Mean	sd	NAs	*p* value
11										
Training	4.200	1.072	19.896	8	0.504	0.400	−0.060	3.585	8	0.704
Detraining	−3.700	−1.754	6.130	9		−0.700	0.342	3.772	9	
10										
Detraining	−3.700	−1.600	6.220	7	0.224	−0.700	0.048	3.565	7	0.805
Extension	−0.800	0.659	6.988	11		−0.500	−0.238	4.742	11	
No. of subjects	FVC					FEV1				
	Median	Mean	sd	NAs	*p* value	Median	Mean	sd	NAs	*p* value
11										
Training	0.040	0.008	0.312	6	0.444	0.020	−0.012	0.297	6	0.850
Detraining	0.030	−0.049	0.238	3		−0.025	−0.025	0.212	3	
10										
Detraining	0.030	−0.052	0.247	3	0.598	−0.030	−0.025	0.212	3	0.707
Extension	0.000	−0.013	0.322	8		0.000	0.000	0.309	8	
No. subjects	MIP					MEP				
	Median	Mean	sd	NAs	*p* value	Median	Mean	sd	NAs	*p* value
11										
Training	3.000	3.222	7.361	6	0.032	4.000	1.852	10.981	6	0.746
Detraining	−1.500	−0.933	6.848	3		3.500	2.733	9.270	3	
10										
Detraining	−2.000	−0.926	7.216	3	0.553	3.000	2.852	9.542	3	0.236
Extension	1.000	0.406	9.883	8		−1.500	−0.344	10.953	8	

Longitudinal analysis of forced vital capacity (FVC), expiratory volume in the first second (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and capillary blood gas analysis, including oximetry and capnometry

For the comparison of detraining to extension period, the values in the median, mean and standard deviation change because we have excluded one patient that was lost to follow-up in the extension period

on eight LOPD patients published by Goksen Kuran Aslan in 2016, both MIP and MEP increased significantly after 8 weeks inspiratory muscle training (MIP by a mean of 6.0 cmH_2O and MEP by a mean of 12.2 cmH_2O) [40]. Subjects performed an IMT for 15 min twice a day at least 5 days per week (80 sessions per subject), using a threshold inspiratory muscle trainer with an inspiratory resistance range from 9 to 41 cmH_2O. The initial resistance was set to 30% of baseline MIP and increased by 2 cmH_2O every week. Except for the "social isolation" subscore of Nottingham Health Profile, all other outcome measures were non-significant, including spirometry measurements and Pittsburgh Sleep Quality Index [40]. Jevnikar et al. conducted the only long-term study on IMT in patients with LOPD in 2015 [41]. Eight patients performed 24 months inspiratory threshold training. One training cycle consisted of a 1-min inspiratory load (30% of baseline MIP) and 2 min of deep slow breathing. In total, patients were advised to perform 15 training cycles per day (45 min) 7 days per week at home. MIP increased at every measured time point every 3 months in the first year and after 24 months significantly (MIP after 24 months + 17.8%, $p = 0.0008$). However, secondary outcomes such as MEP, grade of dyspnea and Gardner–Medwin–Walton score did not change significantly after 12 months and 2 years of follow-up.

One possible explanation for the lack of impact on the secondary outcome measures might be the type of training. In previous studies as well as in our study, we prescribed only inspiratory muscle training, which is by far the most commonly used and researched method of IMT [36]. In our training regimen, a resistive load was used to enhance diaphragmatic strength, as this has a major impact on LOPD. On the other hand, threshold load and normocapnic hyperpnea are known to increase endurance. Combining the training of inspiratory muscle strength and inspiratory endurance might contribute to a more efficient improvement of respiratory muscle weakness and improve secondary outcome measures and quality of life in LOPD.

Our study has some limitations, including an absence of a placebo group (e.g., sham training) and a small number of patients, as it is often the case when conducting clinical trials in patients with rare diseases. Moreover, we did not perform non-volitional tests of respiratory muscle strength. This might have an impact on the reliability of the test results, as spirometry assessments are highly dependent on the patient's motivation and cooperation. For an objective evaluation of performed IMT, we decided to use the commercially available, digital respiratory training device RespifitS®. However, data readout was limited due to corrupt data storage with a relatively high rate, which impedes an unbiased statistical evaluation of training efficacy. Furthermore, we have used an IMT protocol based on published protocols for patients with COPD, which might not be ideally appropriate for patients with LOPD. However, as existing training protocols are highly variable and effects of RMT have not yet been investigated in larger cohorts, a randomized, controlled multicenter study could help to define recommendations for respiratory treatment in patients with LOPD.

Overall, in consideration of published data and our results, frequent IMT improves MIP, and therefore improves diaphragmatic weakness. However, neither our nor previously published studies could show that this improvement had a significant impact on spirometry measurements (FVC, FEV1), oximetry, capnometry, motor function or patient´s self-reported outcomes. Retrospective analysis of historical spirometry measurements from our subjects did not indicate any significant difference in the annual decline of FVC or FEV1 before and after 1 year of IMT. Despite decreasing motivation with a declining number of performed IMT over time, MIP was the only stable measurement throughout the study and showed the highest increase after 52 weeks, suggesting that even a lower target of IMT per week may help to prevent a decline in diaphragm weakness. It may be important to highlight that none of the studies mentioned above has analyzed the efficacy of IMT based on characteristics such as age, gender, duration of symptoms, duration of ERT or grade of respiratory insufficiency at baseline. This is obvious in clinical trials dealing with small sample sizes in rare diseases, which makes a comprehensive statistical analysis, e.g., regression or subgroup analysis inappropriate.

All previous clinical trials have been performed in patients receiving ERT, so data on the efficacy of IMT in untreated patients were absent. Assuming an estimated decline of 3.2% in MIP and 2.3% in FVC in untreated patients with LOPD [13, 14] and a progressive decline of respiratory muscle function in about one-third of adults on ERT [42], a recurrent IMT might stabilize or decelerate the decline of respiratory muscle function, as long as the training is performed consequently and long enough. This is even more true for patients who are unable to receive ERT. Therefore, we recommend respiratory muscle training in patients with LOPD. Our data also confirm that increasing the resistance in IMT does not increase the number of side effects related to the IMT, as long as the training is supervised and resistance is individually adjusted to the patient´s perceived grade of exhaustion.

Conclusion

Frequent IMT may be beneficial for patients with LOPD and clinical or spirometry signs of respiratory insufficiency. The level of inspiratory resistance should start at 30% of MIP and further increased as long as the Borg score is below seven. This may reduce the occurrence of adverse events. Based on our results and previously reported study results, at the moment it is impossible to provide a precise number of a minimum of IMT intervals needed per week to increase the strength of inspiratory muscles. Controlled, randomized long-term multicenter trials with larger sample size and a combination of inspiratory muscle strength and endurance training will help to define recommendations for respiratory treatment in patients with LOPD more precisely and evaluate the effects of frequent IMT over a long period of training.

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Compliance with ethical standards

Conflicts of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics committee of the Ludwig-Maximilians-University Munich, Germany (vote no. 689/16).

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