The effect of respiratory muscle endurance training in patients with myasthenia gravis

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Abstract

We tested the effect of a home-based respiratory muscle endurance training in patients with mild to moderate generalized myasthenia gravis (MG) on Besinger score, lung function and respiratory muscle endurance. Ten patients performed respiratory muscle endurance training in form of normocapnic hyperpnea training at 50–60% of their maximal voluntary ventilation over 4–6 weeks. MG score, lung function and respiratory endurance were assessed before and after training period. The training significantly increased respiratory endurance from 8.4 ± 0.9 min to 17.1 ± 1.3 min (\(p < 0.001\)) and total ventilatory volume from 555 ± 87L to 1081 ± 127L (\(p = 0.004\)). About 25% of this gain was lost after 3–5 months of detraining. The remaining 75% gain might result from improved neuromuscular coordination rather than muscular training. MG score and lung function, however, did not change. Patients assessed the training effects on physical fitness and respiration as positive. In conclusion, respiratory muscle endurance training can be useful for MG patients as it is enhancing respiratory muscle endurance.

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1. Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular synapse characterized by reduced muscle strength and endurance [1–4]. Respiratory muscles may also be affected as expressed, for example, by a reduction of maximal voluntary ventilation (MVV) or by a rapid and shallow breathing pattern at rest [2,5,6]. MG patients often show a characteristic “myasthenic pattern” of decreasing respiratory volumes during MVV [6] and reduced respiratory muscle endurance despite normal spirometric values [3]. Hence, their ability to sustain increased ventilation such as in situations of physical activity can be reduced and may even compromise the patients’ daily life. Larger impairment of respiratory muscles means a serious aggravation of the disease associated with an additional deterioration of the patients’ functional capacity. Respiratory failure can develop as one of the most severe complications of respiratory muscle weakness [7,8]. Infections such as bronchopneumonia are the most common precipitating factor of myasthenic crisis [9,10]. Improvement of respi-

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ratory muscle function is therefore an important objective in MG therapy.

During the past decade, exercise therapy has been introduced as a possible adjuvant treatment for MG patients [4,11]. However, to reduce possible respiratory complications of MG, training programs should focus also on specific respiratory muscle training. Only a few studies have investigated the effects of respiratory muscle training in MG patients showing that resistive or threshold inspiratory muscle training, partially combined with specific expiratory muscle training, induced a significant increase in respiratory muscle strength and/or endurance as well as significant alleviation of dyspnea [12–14]. In these cases, respiratory muscle endurance was assessed by progressive inspiratory loading. However, a more relevant problem for MG patients is the maintenance of elevated levels of ventilation over a longer period of time in order to better cope with increased physical activity.

Recently, a portable respiratory muscle endurance training device was developed allowing subjects to perform normocapnic hyperpnea at home without the need of a CO₂ gas tank to avoid hyperventilation [15]. In healthy untrained or trained subjects, this training did not only increase respiratory muscle endurance and cycling endurance [15–19], but also decreased respiratory muscle fatigue during exercise [20]. Respiratory muscle endurance training might also be the most appropriate kind of training to improve respiratory muscle endurance in MG patients. The present study was therefore designed to test the applicability of this training to patients with mild to moderate MG and to assess the training effects on MG symptoms, lung function and respiratory endurance.

2. Methods

2.1. Subjects

The patients included in this study were regularly consulting a neurologist specialized in treatment of MG who was involved in this study (IB). We chose 20 patients with mild to moderate generalized MG (degree 1–3 according to Oosterhuis classification [1]; II–IV according to Osserman classification [21]) as possible participants. They had been suffering from MG for 1–14 years. Patients with ocular symptoms only and hospitalized patients were excluded. Six of the pre-selected patients resigned from participation in the training study due to problems with transportation or with their personal schedule. Four patients tried the training but did not cope with the technique and the training intensity. Characteristics of the participating 10 patients are given in Table 1. Except for four patients with arterial hypertension, the patients had no additional chronic diseases, in particular, no respiratory diseases. None of the patients smoked at present. Three patients (8, 11 and 14) were ex-smokers but had ceased smoking at least 10 years before. All participating patients gave their written informed consent. The study was approved by the local Ethics Committee.

2.2. Study protocol

2.2.1. Introductory session

On this first day, all testing and training details were explained and demonstrated to the patients. The patients were instructed how to use the training device and tried the technique for several minutes. At the end

<table>
<thead>
<tr>
<th>Patient (no.)</th>
<th>Gender</th>
<th>Age (years)</th>
<th>BMI (kg m⁻²)</th>
<th>Degree of MG</th>
<th>Years since diagnosis</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>F</td>
<td>49</td>
<td>23.89</td>
<td>IIa</td>
<td>9</td>
<td>150 100</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>31</td>
<td>23.18</td>
<td>IIa</td>
<td>2</td>
<td>180 100</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>30</td>
<td>20.17</td>
<td>IIb</td>
<td>6</td>
<td>60 50</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>62</td>
<td>31.38</td>
<td>IIa</td>
<td>4</td>
<td>90 100</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>73</td>
<td>26.51</td>
<td>IIa</td>
<td>1</td>
<td>90 100</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>67</td>
<td>21.26</td>
<td>IIa</td>
<td>1</td>
<td>180 100</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>59</td>
<td>27.12</td>
<td>IIa</td>
<td>5</td>
<td>420 100</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>60</td>
<td>29.41</td>
<td>IIa</td>
<td>14</td>
<td>210 0</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>49</td>
<td>24.69</td>
<td>IIa</td>
<td>10</td>
<td>180 0</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>52</td>
<td>26.45</td>
<td>IIa</td>
<td>1</td>
<td>180 0</td>
</tr>
</tbody>
</table>

Mean (SEM) 53 (4.5) 25.4 (1.1) 1.8 (0.2) 2.0 (0.0) 5 (1.4) 177 (31) 61 (15)

Degree of myasthenia gravis (MG): OO classification according to Oosterhuis [1]; OM classification according to Osserman [21]; medication: ChEI cholinesterase inhibitor (pyridostigmin bromide), IT immunotherapy (azathioprin). Except for reduction of ChEI dose of patient 11 from 210 to 150 mg/d during the detraining period, medication was not changed throughout the time of the study. Mean values (SEM) are given in the bottom lines.

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of the session they took the device home for a week to practice the technique for about 10 min per day. We contacted them every second day to help in case of problems. After a break of 6–12 weeks, the pre-training (baseline) testing period (B) was started.

2.2.2. Pre-training testing period

The tests contained assessment of the MG score (Besinger score), lung function and respiratory muscle endurance. The Besinger score for quantifying disturbances of muscular endurance in MG includes motor function tests (e.g. arm or leg holding time) and assessment of various everyday motor activities such as speaking or chewing [22]. Values range from 0 (minimal impairment) to 4 (severe impairment). Lung function testing (Masterscreen bodydiff, Viasys Healthcare, Höchberg, Germany) included assessment of vital capacity (VC), forced expiratory volume in 1 s (FEV1), peak expiratory flow (PEF), MVV and maximal inspiratory pressure (PImax). The best values out of three trials were chosen. For the respiratory endurance test, patients used their training device connected to a metabolic cart (Oxycon alpha, Viasys Healthcare, Höchberg, Germany). They were instructed to breathe 25–40 times per minute with a tidal volume (VT) ranging between 50% and 75% of VC in order to induce test termination due to task failure after a maximum of 10–12 min. An experimenter encouraged them to breathe faster or slower if necessary. Criteria to terminate the test were patients’ perception of exhaustion or a reduction in ventilation (VE) by more than 10% of the target for 1 min. We measured endurance time (Tlim; time until test termination) and endurance volume (Vlim; total ventilation during the test, calculated as Tlim multiplied by the average VT). Each endurance test was preceded by recording resting breathing over 7–10 min. The breathing pattern characterized by VE, VT, fR, inspiration time (Tin), expiration time (Tex) and VT/Tin was analyzed as well.

The test series started with a respiratory endurance test on day 1. The Besinger score was estimated after a pause of at least 90 min. After a 48–72 h break, lung function was tested. After another break of 48–96 h, patients accomplished a second respiratory endurance test. If the performance of these tests was not satisfactory, a third endurance test was carried out 48–72 h later. The best trial was evaluated. Lung function measurements were performed in the morning, all other tests in the afternoon. The entire test period lasted 7–10 days.

2.2.3. Training period

Training started 2–4 days after completion of all pre-training tests. All patients accomplished 20 training sessions in a period of 4–6 weeks with about five training days and two resting days per week. The training was performed as normocapnic hyperpnea training over 30 min per training session. Normocapnia was achieved by partial rebreathing. Patients used a portable device as described in detail by Markov et al. [18]. In brief, the device consisted of a rebreathing bag and tubing with a hole allowing to breathe in and out to fresh air. Target VE was determined according to the results of the pre-training respiratory endurance test and ranged between 50% and 60% of the individual MVV with VT being 50–60% of VC and respiratory rate (fR) 25–35 breaths min⁻¹. VT was controlled by the size of the rebreathing bag, and fR was paced by a metronome. Patients were instructed to perform the training at home always at the same time of day and at a constant time interval after medication. After each training session, they had to fill in a short questionnaire regarding changes in MG symptoms, occurrence and degree of air hunger and respiratory effort.

Patients were required to report to the laboratory at least two times during the training period to perform a training session with the device connected to the metabolic cart to assure correct settings. The first of these laboratory sessions was carried out after 3–6, the second after 10–15 home training sessions. Additionally, we contacted all patients twice a week to ask for problems with the training or with their MG symptoms.

2.2.4. Post-training testing period

At least six days after completion of the last training session, the post-training test series (P) was carried out in the same way and according to the same schedule as the pre-training test series. All examinations were performed at the same time of day as the pre-training tests. For the respiratory endurance test, VE, VT and fR were set to the same values as in the pre-training test. This test was accomplished at least two times on separate days with the best test being evaluated.

2.2.5. Detraining testing period

Patients were then instructed not to perform similar types of respiratory training during the following 3–5 months (detraining phase). After this period (4.2 ± 0.3 months), all patients returned to the laboratory to perform a final respiratory endurance test (F) and to give a final interview. The main questions of this interview were as follows: (i) How did you perceive training effects on your physical fitness? (ii) How did you perceive training effects on your respiration (respiratory symptoms)? (iii) Would you recommend respiratory training such as the one you have experienced to other patients with myasthenia gravis? Questions regarding the training effects were assessed using visual analogue scales with the midpoint being defined as 0% (no change), the left margin as −100% meaning extremely deteriorated, and the right margin as +100% meaning extremely improved. Recommendation of respiratory training was assessed by the percentage of positive and negative answers.

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2.3. Data analysis

All values are given as mean ± SEM. Comparisons between the three testing periods (i.e. \( T_{\text{lim}} \) and \( V_{\text{lim}} \)) were performed using ANOVA with post-hoc multiple range test based on least significant differences. When only pre-training and post-training tests were compared (i.e. Besinger score, lung function, breathing pattern at rest), the Wilcoxon matched pairs signed ranks test was used. A linear regression analysis between the change in Besinger score and the changes in perceived physical fitness and respiratory symptoms, respectively, was performed.

3. Results

3.1. Training course

All patients completed 20 training sessions with a duration of 30 min per day as required. The mean duration of the training period was 33 ± 2 days. No complications were reported during the total observation period. Likewise, medication was not changed throughout the time of the study with the exception of one patient whose drug dose was reduced by 30% during the detraining period.

3.2. Besinger score of MG symptoms

The patients achieved a pre-training Besinger score of 0.74 ± 0.10. After the training period, the average score was not significantly changed (0.66 ± 0.09). Five patients showed a reduction (i.e. an improvement) by -34 ± 13%, three patients, however, increased their scores by 34 ± 11%. No deterioration in MG symptoms related to respiratory training was reported in the training questionnaire.

3.3. Lung function

Pre-training lung function was normal for all patients with VC being 94.0 ± 3.4%, MVV 98.2 ± 9.1% and FEV\(_1\) 93.8 ± 4.6% predicted. PEF was also normal (86.2 ± 6.1% predicted), whereas PI\(_{\text{max}}\) was slightly reduced (69.6 ± 7.8% predicted). Respiratory muscle endurance training induced no significant changes in lung function (VC: 95.8 ± 3.0%, MVV: 108.5 ± 8.3%, FEV\(_1\): 98.0 ± 4.0%, PEF: 96.2 ± 5.1%, PI\(_{\text{max}}\): 70.0 ± 5.1% predicted). Absolute values are given in Table 2.

3.4. Breathing pattern at rest

In the pre-training tests, we observed a mildly elevated ventilation at rest with \( V_{E} \) of 10.7 ± 0.7 L min\(^{-1}\), \( V_{T} \) of 0.64 ± 0.06 L and \( f_{R} \) of 17.3 ± 1.5 min\(^{-1}\). \( T_{\text{in}} \) and \( T_{\text{ex}} \) were 1.46 ± 0.1 s and 2.01 ± 0.2 s, respectively, and \( V_{E}/T_{\text{in}} \) was 0.4 ± 0.02 L s\(^{-1}\). In the post-training tests, the patients tended to decrease \( f_{R} \) to 15.4 ± 1.6 min\(^{-1}\) (\( p = 0.10 \)) compared to pre-training values while \( V_{E} \) was significantly reduced (9.3 ± 0.9 L min\(^{-1}\); \( p = 0.05 \)) compared to pre-training values. The \( T_{\text{in}} \) to \( T_{\text{ex}} \) ratio remained similar (1.67 ± 0.2 s and 2.22 ± 0.2 s, respectively; \( p > 0.05 \)).

3.5. Respiratory endurance tests

In the pre-training endurance test, patients achieved an average \( T_{\text{lim}} \) of 8.4 ± 0.9 min at an average \( V_{E} \) of 61.2 ± 7.2 L min\(^{-1}\) corresponding to 55.0 ± 2.8% MVV. \( V_{T} \) and \( f_{R} \) were 2.0 ± 0.2 L and 29.4 ± 1.7 min\(^{-1}\), respectively; \( T_{\text{in}} \) was 0.98 ± 0.06 s, \( T_{\text{ex}} \) was 1.10 ± 0.08 s and \( V_{E}/T_{\text{in}} \) was 2.1 ± 0.2 L s\(^{-1}\). The patients’ \( V_{\text{lim}} \) was 555 ± 87 L during \( T_{\text{lim}} \). Respiratory muscle endurance training significantly increased \( T_{\text{lim}} \) to 17.1 ± 1.3 min (\( p < 0.001 \)) and \( V_{\text{lim}} \) to 1081 ± 127 L (\( p = 0.004 \)). The breathing pattern remained unchanged (\( V_{E} \): 63.3 ± 6.5 L min\(^{-1}\), \( V_{T} \): 2.2 ± 0.2 L, \( f_{R} \): 30.0 ± 1.7 min\(^{-1}\), \( T_{\text{in}} \): 0.92 ± 0.05 s, \( T_{\text{ex}} \): 1.12 ± 0.07 s, \( V_{E}/T_{\text{in}} \): 2.4 ± 0.2 L s\(^{-1}\), \( p > 0.05 \)). After a detraining period of 3–5 months, \( T_{\text{lim}} \) was reduced by 29% to 14.6 ± 1.6 min and \( V_{\text{lim}} \) was reduced by 22% to 967 ± 100 L, but both parameters were still significantly elevated compared to pre-training values (Fig. 1). Breathing pattern was similar to that in the preceding tests (\( V_{E} \): 61.6 ± 5.4 L min\(^{-1}\), \( V_{T} \): 2.0 ± 0.1 L, \( f_{R} \): 29.4 ± 1.0 min\(^{-1}\), \( T_{\text{in}} \): 1.00 ± 0.04 s, \( T_{\text{ex}} \): 1.08 ± 0.05 s, \( V_{E}/T_{\text{in}} \): 2.1 ± 0.2 L s\(^{-1}\), \( p > 0.05 \)).

3.6. Final interview

Patients perceived the effort during the respiratory muscle endurance training as moderate to strong. Despite this effort, 8 of 10 patients reported that they felt better during the training period than before, the others

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Table 2

<table>
<thead>
<tr>
<th>Absolute values</th>
<th>VC (L)</th>
<th>FEV(_1) (L)</th>
<th>MVV (L/min)</th>
<th>PEF (L/s)</th>
<th>PI(_{\text{max}}) (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-training</td>
<td>3.63 (0.24)</td>
<td>2.92 (0.23)</td>
<td>112.5 (13.2)</td>
<td>6.50 (0.63)</td>
<td>7.39 (0.82)</td>
</tr>
<tr>
<td>Post-training</td>
<td>3.68 (0.21)</td>
<td>3.02 (0.19)</td>
<td>123.1 (1.7)</td>
<td>7.25 (0.63)</td>
<td>7.43 (0.53)</td>
</tr>
</tbody>
</table>

Data are given as means (SEM). VC vital capacity, FEV\(_1\) forced expiratory volume in 1 s, MVV maximal voluntary ventilation, PEF peak expiratory flow, PI\(_{\text{max}}\) maximal inspiratory pressure. No significant differences between pre-training and post-training values were observed.

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felt no difference. None of the patients reported negative effects. The extent of change in physical fitness was 42.1 ± 7.2% and correlated significantly with the change in Besinger score ($r = -0.76$, $p = 0.01$). Respiratory symptoms were alleviated by 36.0 ± 10.2% and the change correlated significantly with the reduction in Besinger score ($r = -0.86$, $p = 0.001$; Fig. 2). Nine of the 10 patients (4 males and 5 females) stated that they would recommend their respiratory training to other MG patients and that they would repeat such a respiratory training. One female patient answered indecisively.

4. Discussion

Positive effects of specific respiratory muscle training on respiratory muscle strength and endurance were demonstrated for the first time by Leith and Bradley [23] in healthy individuals and by Keens et al. [24] in patients. The majority of research on respiratory muscle training has focused on patients with pulmonary disorders such as cystic fibrosis [24], asthma [25] or chronic obstructive pulmonary disease (COPD) [26]. Since inadequate function of respiratory muscles may often lead to respiratory dysfunction and complications, there is also a strong rationale for a specific training of respiratory muscles in patients with neuromuscular diseases. Respiratory muscle training improved lung function, respiratory muscle strength and/or respiratory muscle endurance in patients with spinal cord injury [27,28], postpolio syndrome [29] or with neuromuscular disorders such as Duchenne’s muscular dystrophy or spinal muscular atrophy [30,31]. In contrast, there is only little experience with specific respiratory training in MG patients [12–14]. To our knowledge, the present study is the first one in MG patients applying respiratory muscle endurance training in form of normocapnic hyperpnea which specifically aims at improving respiratory muscle endurance. Increased respiratory muscle endurance should enable the patients to maintain an increased level of ventilation over a longer period of time such as in situations of physical activity.

In the present study, respiratory muscle endurance training considerably enhanced the ability to sustain hyperpnea as reflected by significant increases in $T_{\text{Lim}}$ and $V_{\text{Lim}}$ to more than twice the pre-training values. About 75% of this effect was still present after a detraining period of 3–5 months suggesting that this gain resulted from improved neuromuscular coordination while the 25% gain that was lost after the detraining period could possibly be considered to be a muscular training effect.

The increased respiratory endurance was associated with enhancement of perceived physical fitness and alleviation of respiratory symptoms. Although the objective Besinger score of MG symptoms did not change significantly, it was significantly correlated with the change in perceived physical fitness and respiratory symptoms. Patients became aware of these subjective improvements of their general state very early in the training period, after initial reservations and some problems due to the intense training effort. Numerous actions of daily living were perceived as being less exhaustive which was reflected in the positive assessment of training effects on physical fitness and respiration. The latter was particularly mentioned by patients who had experienced respiratory problems in their past. We consider the tendency to a lower respiratory rate at rest to be a possible reason for this subjective improvement as a rapid shallow breathing pattern is characteristic for patients with moderate MG [2,5] and is thought to be due to respiratory muscle weakness. Moreover, patients regarded the experience of actively dealing with their respiration as a valuable advantage of respiratory training. In the final interview, nine of the ten patients stated that they would repeat such a respiratory training. Meanwhile, five of them (2 males and 3 females) participate in a subsequent respiratory muscle endurance training study.

Lung function did not significantly change after respiratory muscle endurance training similar to earlier studies in healthy subjects [15–17,32]. In MG patients, we
particularly did not expect improvements in VC, FEV$_1$, PEF and inspiratory pressure since these measures are based on short maneuvers with maximal effort – an ability that was not reduced in our patient population. However, Weiner and colleagues demonstrated that three months of inspiratory muscle strength training performed six times per week significantly improved VC and FEV$_1$ in MG patients [12]. This might be explained by the training specificity of different types of respiratory muscle training as described by Leith and Bradley [23] who showed respiratory muscle strength training to mainly improve maximal force while respiratory muscle endurance training improved endurance but not maximal force. Moreover, training effects also depend on duration and intensity of training. A recent study applying interval-based inspiratory muscle training three times a week over 8 weeks did not show any changes in lung function in MG patients [14].

The most pronounced effect of the present training was a significant improvement in respiratory endurance, i.e. in $T_{1\text{lim}}$ and $V_{1\text{lim}}$. Improved respiratory endurance has a greater importance than an improvement of lung function in MG patients. Weakness and fatigue of respiratory muscles are responsible for dyspnea and reduced exercise tolerance and thus, can compromise the quality of life and increase the risk of respiratory failure [8]. The subjectively perceived benefit of the training is reflected best in the fact that five of the patients participate in a subsequent training study.

4.1. Limitations of the study

Patients were selected by a neurologist who knew the patients from diagnosis and saw them regularly three to four times per year. Nevertheless, some patients revealed considerable difficulties in the ability to perform respiratory muscle endurance training but these were unrelated to the neurologist’s assessment of MG degree. These patients finally resigned from performing this training. Moreover, the study regimen was strenuous and time-consuming, and several patients who were asked for participation in this study refused. For this reason, no control group could be formed so that the study was carried out as an uncontrolled observational study. Three patients were assessed to be very highly motivated to perform respiratory muscle endurance training due to personal experience with respiratory disturbances. The motivation of the others was estimated as medium to high but transiently decreased in some patients during the familiarization period and the first training units. A control group with similar positive expectations but no neuromuscular training effects on the respiratory system would certainly have enhanced the validity of the results. Despite these limitations, we believe this study to be a good start for further investigations in this direction since it demonstrated that even in patients with a disease of the neuromuscular synapse respiratory muscle endurance training can be performed safely resulting in an improvement of respiratory muscle function.

In conclusion, this study revealed that respiratory muscle endurance training is applicable in many but not all MG patients (independent of the severity of disease). Once the patients are used to the technique and are motivated to perform this strenuous training, positive subjective and objective training effects can be observed after 4–6 weeks.

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