ABSTRACT: Background: Myasthenia gravis (MG) is a specific autoimmune disease characterized by weakness and fatigue. MG may affect also the respiratory muscles causing symptoms that may vary from dyspnea on severe exertion to dyspnea at rest. This study was undertaken in order to determine the effects of respiratory muscle training on respiratory muscle performance, spirometry data and the grade of dyspnea in patients with moderate to severe generalized MG. Methods: Eighteen patients with MG were studied and divided into 2 groups: Group A included 10 patients (3 males and 7 females aged 29-68) with moderate MG, and Group B that included 8 patients (5 males and 3 females aged 21-74) with severe MG. Patients in Group A received both inspiratory and expiratory muscle training for 1/2 h/day, 6 times a week, for 3 months, while patients in Group B followed the same protocol but had inspiratory muscle training only. Results: Mean PI max increased significantly from 56.6 ± 3.9 to 87.0 ± 5.8 cm H2O (p < 0.001) in Group A, and from 28.9 ± 5.9 to 45.5 ± 6.7 cm H2O (p < 0.005) in Group B. The mean PE max also increased significantly in patients in Group A, but remained unchanged in the patients in Group B. The respiratory muscle endurance also increased significantly, from 47.9 ± 4.0 to 72.0 ± 4.2%, p < 0.001, in patients of Group A, and from 26.0 ± 2.9 to 43.4 ± 3.8, p < 0.001, in patients in Group B. The improved respiratory muscle performance was associated with a significant increase in the FEV1 values, and in the FVC values, in patients of both groups. Mean dyspnea index score also increased significantly from 2.6 ± 0.8 to 3.6 ± 0.4 (p < 0.005) in Group A, and from 0.7 ± 0.2 to 2.0 ± 0.2 (p < 0.001) in Group B. Conclusions: Specific inspiratory threshold loading training alone, or combined with specific expiratory training, markedly improved respiratory muscle strength and endurance in patients with MG. This improvement in respiratory muscle performance was associated with improved lung function and decreased dyspnea. Respiratory muscle training may prove useful as a complementary therapy with the aim of reducing dyspnea symptoms, delay the breathing crisis and the need for mechanical ventilation in patients with MG.
due to respiratory muscle involvement depend on the severity of the disease, and may vary from dyspnea on mild to moderate exertion to respiratory failure that require prolonged periods of assisted ventilation. Anticholinesterase therapy, thymectomy and immunosuppression are frequently used in the treatment of MG. However, only a few patients will regain normal function with the therapy.

It is well established that respiratory muscles can be trained for both strength and endurance like other skeletal muscles and several reviews have been published dealing with ventilatory muscle training. Its efficacy has been previously shown in normal subjects, quadriplegics, cystic fibrosis, asthma, patients on chronic hemodialysis, patients undergoing open heart surgery as well as in patients with COPD. However, our research revealed only one study, with a small group of patients, in which the respiratory muscles were trained specifically in patients with MG.

This study was designed in order to assess the effects of respiratory muscle training (RMT) on inspiratory and expiratory muscle strength, endurance, lung function, and dyspnea, in a population of adult MG patients.

**METHODS**

**Patients** Eighteen patients with MG (10 women and 8 men) 21 to 74 yr age (mean ± SEM, 45.4 ± 3.7 yr) were included in the study. The diagnosis of MG was based on a history of fatigability of the motor response to repetitive nerve stimulation and by a decremental response of the amplitude of the motor response to repetitive nerve stimulation and by a positive edrophonium test. Acetylcholine receptor antibodies were investigated in 14 patients, and were present in 12. All had some degree of dyspnea, and were classified functionally according to the Osserman grade (Table 1). The patients were divided into 2 groups: 10 patients that were mildly and moderately affected (of Osserman classification II and III) (Group A) and received both inspiratory muscle and expiratory muscle training, and 8 patients with severe MG (Osserman classification IV) (Group B) received inspiratory muscle training only. All patients were treated by anticholinesterase, 13 had thymectomy, and 11 received steroids (prednisone 20-40 mg on alternate days). No change in drug therapy was allowed during the study. Two patients, in Group B (No. 1, 2) were treated with supplemental oxygen before training.

**Spirometry** Pulmonary functions were assessed by spirometry, performed before, 1 month and 3 months following RMT. The forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1) were measured 3 times on a computerized spirometer (Compact, Vitalograph, Buckingham England) and the best trial is reported.

**Respiratory muscle strength** Respiratory muscle strength was assessed by measuring the maximal inspiratory mouth pressure (PImax) at residual volume (RV) and the maximal expiratory mouth pressure (PEmax) at total lung capacity (TLC) as previously described by Black and Hyatt. The value obtained from the

<table>
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<th>PImax (cm H2O)</th>
<th>PmPeak/PImax (%)</th>
<th>PaO2 mmHg</th>
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| Group B     |     |         |                  |                     |               |                 |         |         |
| 1           | M   | 74      | IV               | 0                   | 10            | 14              | 7       | 12      | 51      | 65      |
| 2           | F   | 43      | IV               | 0                   | 13            | 22              | 10      | 5       | 48      | 80      |
| 3           | F   | 66      | IV               | 1                   | 8             | 26              | 15      | 8       | 65      | 47      |
| 4           | M   | 50      | IV               | 0.5                 | 27            | 27              | 5       | 16      | 60      | 48      |
| 5           | M   | 65      | IV               | 1                   | 47            | 39              | 40      | 56      | 75      | 45      |
| 6           | M   | 21      | IV               | 1                   | 49            | 44              | 41      | 32      | 78      | 61      |
| 7           | F   | 42      | IV               | 1                   | 35            | 51              | 23      | 53      | 68      | 41      |
| 8           | M   | 43      | IV               | 1                   | 41            | 60              | 33      | 26      | 65      | 55      |
| Mean        |     |         |                  |                     | 50.5          | 0.7             | 28.9    | 35.4    | 21.7    | 26.9    | 63.8    | 55.3    | 55      |
| ±SEM        |     |         |                  |                     | ±6.1          | ±0.2            | ±5.9    | ±5.6    | ±5.2    | ±7.0    | ±3.7    | ±4.6    |
best of at least 3 efforts was used.

**Dynamic inspiratory muscle strength** Dynamic inspiratory muscle strength was assessed by measuring the maximal inspiratory mouth pressure (PImax) at residual volume (RV) every 30 seconds and up to 6 measurements.

**Inspiratory muscle endurance** To determine inspiratory muscle endurance a device similar to that proposed by Nickerson and Keens was used. Subjects inspired through a two-way Hans-Rudolph valve whose inspiratory port was connected to a chamber and plunger to which weights could be added externally. Inspiratory elastic work was then increased by the progressive addition of 25 to 100 g weights at 2-min intervals, as was previously described by Martyn and coworkers, until the subjects were exhausted and could no longer inspire. The pressure achieved with the heaviest load (tolerated for at least 60 s) was defined as the peak pressure (PmPeak).

**Training protocol** Subjects in both groups trained daily, six times a week, each session consisted of 1/2 hour training, for three months. The training was performed under the supervision of a physiotherapist.

**Inspiratory muscle training (IMT) and Expiratory muscle training (EMT)** The subjects received IMT with a threshold inspiratory muscle trainer (Threshold™ Inspiratory Muscle Trainer, Healthscan, NJ) and EMT with the same trainer held on the reversed side. Patients in group A received IMT for the first 15 minutes of each session and EMT for the last 15 minutes. The subjects started breathing at a resistance equal to 15% of their PImax or PEmax, for one week. The resistance was then increased incrementally, 5% each session, to reach 60% of their PImax or PEmax at the end of the first month. IMT and EMT were then continued, for the next two months at this level of resistance. Patients in Group B received IMT for the whole session and followed the same protocol.

**Dyspnea index** The clinical rating of dyspnea was graded by a physician, who was blinded to the kind of treatment the patients have received, using the dyspnea index (Appendix A), that was based on two components evoking dyspnea: magnitude of the task which considers mainly isotonic work; and magnitude of effort which considers mainly isometric work. The physician selected one of five grades of dyspnea for each of the two components and the mean of the two numbers is reported. The patients in Group B all had some degree of leg and arm weakness. The physician who graded their degree of dyspnea tried to isolate this weakness from true dyspnea.

**Statistical analysis** The effect of training on lung function, arterial blood gases and respiratory muscle performance was analysed using the two-way repeated measures analysis of variance (Anova). When the overall Anova was significant, post hoc comparisons were made. Chi-square (degree of freedom-1) statistics were used to compare changes in dyspnea index. Pearson correlation coefficients and linear regression analysis allowed comparison between the two regression lines in the dynamic inspiratory muscle strength test. Significance was accepted if p < 0.05.
RESULTS

Respiratory muscle strength The mean effect of the training on the respiratory muscle strength is shown in Figure 1. All patients, in both Group A and Group B, showed an increase in the inspiratory muscle strength, as was assessed by measuring the \( P_{\text{Imax}} \) at RV. Mean \( P_{\text{Imax}} \) increased significantly from 56.6 ± 3.9 to 87.0 ± 5.8 cm H\(_2\)O (\( p < 0.001 \)) in Group A, and from 28.9 ± 5.9 to 45.5 ± 6.7 cm H\(_2\)O (\( p < 0.005 \)) in Group B. The mean \( P_{\text{Emax}} \) also increased significantly in patients in Group A, but remained unchanged in the patients in Group B (from 71.5 ± 3.5 to 86.6 ± 4.7 cm H\(_2\)O, \( p < 0.05 \), and from 28.2 ± 2.6 to 30.1 ± 2.8 cm H\(_2\)O, respectively).

Respiratory muscle endurance The respiratory muscle endurance, as expressed by the relationship between \( P_{\text{Peak}} \) and \( P_{\text{Imax}} \) (\( P_{\text{Imax}} \) following training) also increased significantly, from 47.9 ± 4.0 to 72.0 ± 4.2%, \( p < 0.001 \), in patients of Group A, and from 26.0 ± 2.9 to 43.4 ± 3.8, \( p < 0.001 \), in patients in Group B (Figure 2).

Dynamic inspiratory muscle strength The dynamic inspiratory muscle strength test was performed in order to assess the progressive fatigue of the inspiratory muscles while conducting the maximal inspiratory mouth pressure maneuver 6 times with 30 seconds interval. The dynamic test was performed only in patients in Group A. It was found that not only the \( P_{\text{Imax}} \) was significantly improved, for every single measurement, but the decline in \( P_{\text{Imax}} \) that was noted for repetitive measurements, was significantly attenuated (difference between regression lines- \( p < 0.05 \)) (Figure 3).

Spirometry The effect of the training programs on lung function data are shown in Figure 4. There was a significant increase in the FEV\(_1\) values, from 77.3 ± 2.6 to 88.0 ± 2.2% of predicted normal values, \( p < 0.005 \), in patients of Group A, and from 28.9 ± 5.9 to 45.5 ± 6.7, \( p < 0.005 \), in patients in Group B, and in the FVC values, from 76.2 ± 1.8 to 88.1 ± 2.0, \( p < 0.005 \), in patients of Group A, and from 35.4 ± 5.6 to 53.9 ± 5.0, \( p < 0.001 \), in patients in Group B.

Arterial blood gases \( P_{\text{O2}} \) and \( P_{\text{CO2}} \) remained almost unchanged, following training, in Group A. However, mean \( P_{\text{O2}} \) increased significantly, from 63.8 ± 3.7 to 72.7 ± 4.0 Torr (\( p < 0.005 \)), and the mean \( P_{\text{CO2}} \) decreased significantly, from 55.3 ± 4.6 to 49.8 ± 3.6 Torr (\( p < 0.05 \)) (Figure 5).

Dyspnea index The clinical rating of dyspnea was assessed before and after the training period. The mean dyspnea index score increased significantly from 2.6 ± 0.8 to 3.6 ± 0.4 (\( p < 0.005 \)) in Group A, and from 0.7 ± 0.2 to 2.0 ± 0.2 (\( p < 0.001 \)) in Group B. The results of the individual dyspnea index score are shown in Figure 6. All patients but one (in Group A) improved their dyspnea index score significantly.
Due to reduced inspiratory capacity and expiratory reserve volume, the reduction of lung volume may lead to patchy areas of atelectasis and consequently to ventilation-perfusion mismatch. The weakness of the respiratory muscles in patients with MG is usually symptomatic, depending on the severity of the disease. It may vary from dyspnea only with a vigorous effort to respiratory failure in those patients.

The majority of patients treated with anticholinesterase will improve significantly. However, most of them will remain with impaired respiratory muscle performance and will continue to deteriorate. In addition, overdosage with anticholinesterase treatment may result in increased muscle weakness. Corticosteroids may also improve symptoms in patients with MG, however, there is always the risk of exacerbating muscle weakness, because of myopathic effects.

Patients with MG, not only may have variable degree of dyspnea, but may exhibit respiratory failure either spontaneously or secondary to intercurrent infection, emotional trauma, surgery (especially after thymectomy) or other complications. Improved strength and endurance of the inspiratory muscles may also delay the onset of respiratory muscle fatigue and respiratory failure in those patients.

Leith and Bradley were the first to report that respiratory muscle can be specifically trained in normal persons. Later,
Gross and coworkers\(^7\) showed that resistive breathing training improves inspiratory muscle function in quadriplegics. Since then, many reports have shown the efficacy of inspiratory muscle training in patients with different pulmonary diseases.\(^{13-15,18-22}\) However, IMT or EMT have only been tried in a small group of patients with MG. Our study shows that respiratory muscle training can be performed in patients with MG with significant improvement of respiratory muscle performance, and a reduction in the sense of dyspnea. It may also prevent or delay the need for mechanical ventilation. From this study we can not conclude whether the addition of EMT to IMT is associated with any further improvement. The combination of EMT and IMT was applied only in patients with less severe disease (Group A), while in the patients with more severe disease we tried to reduce the load of training by eliminating the EMT. Nevertheless, both groups improved almost the same amount. Further studies are needed to answer that question.

One may wonder whether the improvement of PI\(_{\text{max}}\) and P\(_{E_{\text{max}}}\) was due to changes in lung volume and not due to true improvement in the performance of the respiratory muscles. Although residual volume could be decreased following training, the magnitude of the improvement in the respiratory muscle performance was much too high to relate it only to lung volume changes. In addition, measurements of respiratory muscle performance are all dependent on the patient’s motivation. Therefore, all patients were trained, to get familiar with the measurements, and highly motivated before entering the study, and baseline results were considered only after obtaining the best values in 3 consecutive measurements. We are almost convinced that the increase in these measurements represents true improvement and not just a motivational effect.

In conclusion, we believe that IMT alone or in combination with EMT may provide a complementary and more physiologic therapy, with the aim of reducing dyspnea symptoms in patients with MG. It may also prevent or delay the breathing crisis and the need for mechanical ventilation that is associated with the disease.

**References**