

# Effects of 8-Week, Interval-Based Inspiratory Muscle Training and Breathing Retraining in Patients With Generalized Myasthenia Gravis\*

Guilherme Augusto de Freitas Fregonezi, PT, MSc;  
Vanessa Regiane Resqueti, PT, MSc; Rosa Güell, MD, PhD;  
Jesus Pradas, MD, PhD; and Pere Casan, MD, PhD

**Study objective:** To assess the effect of interval-based inspiratory muscle training (IMT) combined with breathing retraining (BR) in patients with generalized myasthenia gravis (MG) in a partial home program.

**Design:** A randomized controlled trial with blinding of outcome assessment.

**Setting:** A secondary-care respiratory clinic.

**Patients:** Twenty-seven patients with generalized MG were randomized to a control group or a training group.

**Interventions:** The training group underwent interval-based IMT associated with BR (diaphragmatic breathing [DB] and pursed-lips breathing [PLB]) three times a week for 8 weeks. The sessions included 10 min each of DB, interval-based IMT, and PLB. Interval-based IMT consisted of training series interspersed with recovery time. The threshold load was increased from 20 to 60% of maximal inspiratory pressure (P<sub>imax</sub>) over the 8 weeks.

**Measurements and results:** Lung function, respiratory pattern, respiratory muscle strength, respiratory endurance, and thoracic mobility were measured before and after the 8 weeks. The training group improved significantly compared to control group in P<sub>imax</sub> (p = 0.001), maximal expiratory pressure (P<sub>emax</sub>) [p = 0.01], respiratory rate (RR)/tidal volume (V<sub>T</sub>) ratio (p = 0.05), and upper chest wall expansion (p = 0.02) and reduction (p = 0.04). Significant differences were seen in the training group compared to baseline P<sub>imax</sub> (p = 0.001), P<sub>emax</sub> (p = 0.01), maximal voluntary ventilation (p = 0.02), RR/V<sub>T</sub> ratio (p = 0.003), V<sub>T</sub> (p = 0.02), RR (p = 0.01), total time of RR (p = 0.01), and upper chest wall expansion (p = 0.005) and reduction (p = 0.005). No significant improvement was seen in lower chest wall or lung function.

**Conclusions:** The partial home program of interval-based IMT associated with BR is feasible and effective in patients with generalized MG. Improvements in respiratory muscle strength, chest wall mobility, respiratory pattern, and respiratory endurance were observed.

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**Key words:** breathing exercises; myasthenia gravis; respiratory muscle training

**Abbreviations:** BR = breathing retraining; DB = diaphragmatic breathing; HRQL = health-related quality of life; IMT = inspiratory muscle training; MG = myasthenia gravis; MVV = maximal voluntary ventilation; P<sub>emax</sub> = maximal expiratory pressure; P<sub>imax</sub> = maximal inspiratory pressure; PLB = pursed-lips breathing; RR = respiratory rate; TLC = total lung capacity; TR<sub>TOT</sub> = total time of respiratory rate; V<sub>E</sub> = minute ventilation; V<sub>T</sub> = tidal volume

A decrease in respiratory strength and endurance has been established in patients with generalized myasthenia gravis (MG).<sup>1–5</sup> Several peripheral fac-

tors are considered to be involved, such as a defect in neuromuscular transmission, steroid myopathy or necrosis, atrophy, and accumulation of lymphocytes in muscle.<sup>6,7</sup> Respiratory muscle deterioration in generalized MG causes changes in breathing pat-

\*From the Departments of Pneumology (Drs. Fregonezi, Resqueti, Güell and Casan) and Neurology (Dr. Pradas), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

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Correspondence to: Guilherme Augusto de Freitas Fregonezi, PT, MSc, Departament de Pneumologia, Àrea de Rehabilitación Respiratoria, Hospital de la Santa Creu i de Sant Pau Av, Sant Antoni Maria Claret, 167 08025, Barcelona, Spain; e-mail: [gfreitas@hsp.santpau.es](mailto:gfreitas@hsp.santpau.es)

terns.<sup>8,9</sup> Inspiratory muscle training (IMT) has proven useful in improving respiratory muscle function in numerous illnesses in which muscular weakness may determine morbidity and mortality.<sup>10–17</sup> IMT has also contributed to successful weaning from invasive mechanical ventilation in patients without MG who have had unsuccessful weaning attempts.<sup>18,19</sup> Indications of IMT benefits in MG patients have been reported, but only in two non-randomized studies.<sup>20,21</sup> Interval-based training has proven to be an efficient method in maximizing training in healthy individuals and exercise training in COPD rehabilitation.<sup>22–25</sup> It has also been found effective when applied to inspiratory muscles in patients with COPD.<sup>26–28</sup>

Studies performed using breathing retraining (BR)—diaphragmatic breathing (DB) and pursed-lips breathing (PLB)—have demonstrated a clear improvement in respiratory patterns, mainly due to increases in tidal volume (VT) and minute ventilation ( $\dot{V}_E$ ), and decreases in respiratory rate (RR).<sup>29–32</sup> Nevertheless, no studies have demonstrated the benefits of BR in associated with interval-based IMT in patients with MG.

We hypothesized that an IMT program using interval-based training principles associated with BR could improve respiratory strength, respiratory endurance, thoracic mobility, and respiratory pattern in patients with generalized MG. Considering the tendency to muscular fatigue and weakness in MG, we applied interval-based IMT on the interval training principles, with loads progressing from low-to-moderate intensities. The aim of this randomized controlled trial was to analyze the effects of interval-based IMT-associated BR on lung function, respiratory pattern, respiratory strength, respiratory endurance, and thoracic mobility in generalized MG.

## MATERIALS AND METHODS

### Subjects

Patients with stable generalized MG (subclass IIa and IIb) according to the classification of Osserman and Genkins<sup>33</sup> were recruited from the neuromuscular section of the neurology department. The inclusion criteria were as follows: (1) age  $\leq 75$  years; (2) 60% of maximal inspiratory pressure (P<sub>imax</sub>), not surpassing the maximum value of valve resistance (41 cm H<sub>2</sub>O); (3) stable respiratory and neurologic clinical condition without myasthenia crises in the last 2 months; and (4) no other significant diseases that could inhibit completion of training. The hospital ethics committee approved the study, and all patients gave informed consent.

### Study Design

In this prospective randomized trial, patients were allocated to either a control group or a training group. Conventional medical

treatment for patients with MG was established in both groups by a neurologist. The same physician evaluated neurologic condition before and after 8 weeks to confirm there were no changes in overall severity. Therapy at usual doses, including pyridostigmine bromide, azathioprine, and prednisone, was unchanged throughout the study. The control group received one BR (DB and PLB) session and education about energy conservation at the first visit and were encouraged to use these techniques or contact the team when necessary. The training group received a training program described below.

All patients were encouraged to contact their physician or neurologist at any time if a medical problem arose. Patients in both groups were evaluated at baseline and after 8 weeks. The technicians who collected data for outcome measures were blinded to a patient's allocation.

### Training Program

We designed a partial home training program that consisted of interval-based IMT combined with DB and PLB. The IMT protocol was designed to respect skeletal muscle pathophysiology in MG. A preprogram training period of 3 days was completed to introduce interval-based IMT, with a minimal load and BR. Training was performed at the respiratory rehabilitation section of the Hospital de la Santa Creu i Sant Pau (Respiratory Department). The patients performed the training three times a week, once at the hospital and twice at home. The training continued over 8 weeks and was always supervised by the same physiotherapist. The duration of each session was 45 min and consisted of 10 min of DB, followed by 10-min interval-based IMT and 10 min of PLB. The patients had a 5-min rest before proceeding to the next 10-min task. Interval-based IMT was performed through the valve (Threshold IMT, Inspiratory Muscle Trainer; Respironics; Cedar Grove, NJ).

All patients began with an initial load of 20% of the P<sub>imax</sub> values. This was increased to 30% in the third week, 45% in the fifth week, and 60% in the seventh. Interval-based IMT series were interspersed with recovery times. Total IMT time was always 10 min, and recovery between series was 2 min. In the first, second, and third weeks, training consisted of five IMT series of 2 min. In the fourth, fifth, and sixth weeks, training consisted of four IMT series of 2, 3, 3, and 2 min. In the seventh and eighth weeks, training consisted of three IMT series of 3, 4, and 3 min. The total recovery time between training decreased from 8 min in the first week to 4 min in the last week.

### Outcome Measures

**Pulmonary Function and Respiratory Pattern:** Lung function testing included FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC indexes, and maximal voluntary ventilation (MVV)<sup>34</sup> using spirometry (Datospir 91; SibelMED; Barcelona, Spain). Lung volumes, inspiratory capacity, total lung capacity (TLC), and residual volume were determined by the helium dilution technique, and lung diffusing capacity was calculated by the single-breath method<sup>34</sup> (PFL2450; SensorMedics; Yorba Linda, CA). Pulmonary function values were based on the best of three efforts. The respiratory pattern was studied by  $\dot{V}_E$ , VT, RR, and total time of RR (TR<sub>OT</sub>) [Pulmonary Lung Function 2450; SensorMedics].

**Respiratory Strengths:** Respiratory pressure was measured under static conditions, with P<sub>imax</sub> at functional residual capacity and maximal expiratory pressure (PE<sub>max</sub>) at TLC. Both measurements were made using a manometer (model 163; SibelMED) using the method of Black and Hyatt.<sup>35</sup>

**Thoracic Mobility:** Chest wall expansion and reduction were evaluated with the standard method.<sup>36</sup> A flat tape was placed

around the patient's chest and with the arms down, the patient was asked to breathe out as much as possible while the measuring tape was drawn taut, and the chest circumference was measured (E1 = expiration one). The tape was then released, and patient was asked to breathe in as deeply as possible (I = inspiration). For the last measurement, patients were again asked to breathe out as far as possible (E2 = expiration two). Measurements were made at the axillary level for the upper chest wall and at the xiphisternum for the lower chest wall. All measurements were performed twice, and the average was used. Indexes of chest wall expansion were calculated by  $I - E1$  and the chest wall reduction by  $I - E2$ .

**Health-Related Quality of Life:** The short form-36 is a general questionnaire that measures health-related quality of life (HRQL) and covers nine domains: physical functioning, role physical, role emotional, social functioning, general health perceptions, mental health, bodily pain, vitality, and overall HRQL.<sup>37</sup> For all measures, scores were transformed linearly to scales of 0 to 100, with 0 indicating maximal impairment and 100 indicating minimal impairment.

#### Data Analysis

Data are presented as mean, SD, and range. To compare baseline values between groups, an independent *t* test was used, and a  $\chi^2$  test was applied to compare sex, the number of patients who had undergone thymectomy, and MG severity. The interaction of time and training effects, and the increases in load applied over 8 weeks were evaluated by repeated analysis of variance using the baseline score as a covariate. A paired *t* test was used to compare the data before and after the 8 weeks in the training group. The level of significance used for the tests was 5% ( $p \leq 0.05$ ), and the approach was two sided.

## RESULTS

Twenty-nine subjects were recruited into the study. Two subjects withdrew during the preprogram training period, one due to a myasthenia crisis and the other due to associated disease (lung tumor). Twenty-seven subjects (16 women, 11 men; age range, 33 to 75 years; mean  $\pm$  SD age,  $64 \pm 10$  years; FVC,  $79 \pm 13\%$  predicted value; FEV<sub>1</sub>,  $81 \pm 17\%$  predicted value; body mass index,  $28 \pm 3$ ) completed all the study requirements. No significant differences were found in the therapy in the two groups. The control group received azathioprine,  $145 \pm 13$  mg/d, vs  $137 \pm 37$  mg/d ( $p = 0.72$ ) in the training group; pyridostigmine bromine,  $405 \pm 80$  mg/d, vs  $310 \pm 60$  mg/d ( $p = 0.73$ ) in the control group; and prednisone,  $38 \pm 8$  mg, vs  $42 \pm 11$  mg in the control group ( $p = 0.73$ ). The severity of myasthenia gravis was unchanged over the 8 weeks. The mean  $\pm$  SD and paired baseline data groups (Table 1) showed no statistical difference in baseline values between groups.

#### Pulmonary Function and Respiratory Pattern

Spirometry values and lung volume data were unchanged by the 8-week training program (Table

**Table 1—Patient Characteristics\***

Characteristics	Control Group (n = 13)	Training Group (n = 14)	p Value
Male/female gender	6/7	5/9	0.873†
Age, yr	61 $\pm$ 12	67 $\pm$ 10	0.129
Thymectomy, yes/no	5/8	4/10	0.892†
MG severity, IIa/Iib	6/8	7/6	0.706†
P <sub>imax</sub> , cm H <sub>2</sub> O	61 $\pm$ 15	56 $\pm$ 19	0.485
PE <sub>max</sub> , cm H <sub>2</sub> O	116 $\pm$ 26	102 $\pm$ 34	0.316
MVV, L/min	79 $\pm$ 24	71 $\pm$ 26	0.510
$\dot{V}_E$ , L/min	11 $\pm$ 2.6	10.1 $\pm$ 2.7	0.627
V <sub>T</sub> , L	0.6 $\pm$ 0.2	0.6 $\pm$ 0.2	0.384
RR, breaths/min	19 $\pm$ 6	21 $\pm$ 6	0.422
TTOT, s	3.8 $\pm$ 1.3	3.2 $\pm$ 0.9	0.303
FVC, L	3 $\pm$ 0.8	2.7 $\pm$ 0.8	0.360
FEV <sub>1</sub> , L	2.3 $\pm$ 0.7	1.9 $\pm$ 0.7	0.310

\*Data are presented as Mean  $\pm$  SD or No.

† $\chi^2$  test.

2). The respiratory pattern improved with training, as evidenced by the RR/V<sub>T</sub> ratio, which showed a significant mean decrease of 24% in the training group as compared to a 7% increase in the control group. The RR/V<sub>T</sub> ratio showed a significant decrease in comparison to its baseline value ( $p = 0.003$ ) and in comparison to the control group ( $p = 0.05$ ). The training group showed a mean increase of 25% in TTOT ( $3 \pm 1.2$  to  $4 \pm 1.6$  s,  $p < 0.01$ ), 24% in V<sub>T</sub> ( $0.56 \pm 0.2$  to  $0.7 \pm 0.3$  L/min,  $p = 0.02$ ), and a decrease of 14% in RR ( $21 \pm 7$  to  $18 \pm 7$  breaths/min,  $p = 0.01$ ). This was statistically significant compared to the baseline value. Pulmonary function and respiratory pattern data of the control group and the training group are shown in Table 2.

#### IMT Protocol

A significant increase was seen in the loads applied over the 8 weeks:  $11 \pm 4$  cm H<sub>2</sub>O (20% of initial P<sub>imax</sub>) in the first and second weeks,  $17 \pm 5$  cm H<sub>2</sub>O (30% of initial P<sub>imax</sub>) in the third and fourth weeks,  $25 \pm 8$  cm H<sub>2</sub>O (45% of initial P<sub>imax</sub>) in the fifth and sixth weeks, and  $33 \pm 11$  cm H<sub>2</sub>O (60% of initial P<sub>imax</sub>) in the seventh and eighth weeks.

#### Respiratory Muscle Function

Inspiratory muscle strength (P<sub>imax</sub>) increased significantly in the training group after 8 weeks ( $56 \pm 22$  to  $71 \pm 27$  cm H<sub>2</sub>O) compared to baseline values ( $p = 0.001$ ) and in comparison with the control group ( $p = 0.001$ ). The P<sub>imax</sub> increase was 27% in training group. The P<sub>imax</sub> in the control group remained unchanged after 8 weeks. Expiratory mus-

**Table 2—Spirometry, Lung Volume, and Respiratory Pattern\***

Variables	Control Group		Training Group	
	Before	After	Before	After
FVC, L	3 ± 0.8	3 ± 0.8	2.7 ± 0.8	2.8 ± 0.8
FEV <sub>1</sub> , L	2.3 ± 0.8	2.3 ± 0.8	1.9 ± 0.8	2.0 ± 0.8
TLC, L	4.7 ± 1.2	4.7 ± 1.2	4.3 ± 1.2	4.5 ± 1.1
Residual volume, L	1.6 ± 0.3	1.7 ± 0.4	1.6 ± 0.3	1.7 ± 0.4
Inspiratory capacity, L	2.3 ± 0.6	2.2 ± 0.6	2.0 ± 0.7	2.1 ± 0.8
VE, L/min	10.8 ± 3.3	10 ± 2.1	10.2 ± 3.0	11.3 ± 4.7
VT, L	0.62 ± 0.2	0.64 ± 0.2	0.56 ± 0.2	0.7 ± 0.3†
RR, breaths/min	18.7 ± 7.8	18.3 ± 7.8	21.1 ± 7.5	18 ± 7.4
RR/VT, breaths/L/min	35.5 ± 24	38.2 ± 34	51.2 ± 43	38.5 ± 34††
TROT, s	3.8 ± 1.6	3.9 ± 1.7	3.2 ± 1.2	4.0 ± 1.6†

\*Data are presented as mean ± SD.

†p < 0.05 for both groups in comparison to its baseline value.

†p < 0.05 for group training in comparison to its baseline value.

cles strength (PE<sub>max</sub>) showed an increase of 12% after 8 weeks (103 ± 41 to 115 ± 40 cm H<sub>2</sub>O), significant in relation to the baseline values (p = 0.01) and as compared to the control group (p = 0.01). The PE<sub>max</sub> in the control group showed a slight, nonstatistically significant decrease after 8 weeks (117 ± 31 to 114 ± 35 cm H<sub>2</sub>O). No significant differences were seen in respiratory muscle endurance in the training group as compared to the control group. The increase in MVV was 8% in the training group, and a significant improvement was found in relation its baseline value (71 ± 34 to 77 ± 32 L/min, p = 0.02). The MVV remained unchanged after 8 weeks in the control group. The means of P<sub>imax</sub>, PE<sub>max</sub>, and MVV in the control

group and the training group before and after 8 weeks are shown in Figure 1.

#### Thoracic Mobility

Upper chest wall expansion and reduction increased significantly after 8 weeks in the training group by 44% (5.9 ± 2.5 to 8.6 ± 1.8 cm) and 43% (6.2 ± 2.7 to 8.8 ± 1.9 cm), respectively. This was statistically significant with respect to the control group (p = 0.02 and p = 0.04) and in relation to baseline values (p = 0.005 and p = 0.004). Lower chest wall expansion and reduction improved by 44% (5 ± 4 to 8 ± 3 cm) and 41% (5 ± 4 to 7 ± 3 cm), respectively, but no significance was found with

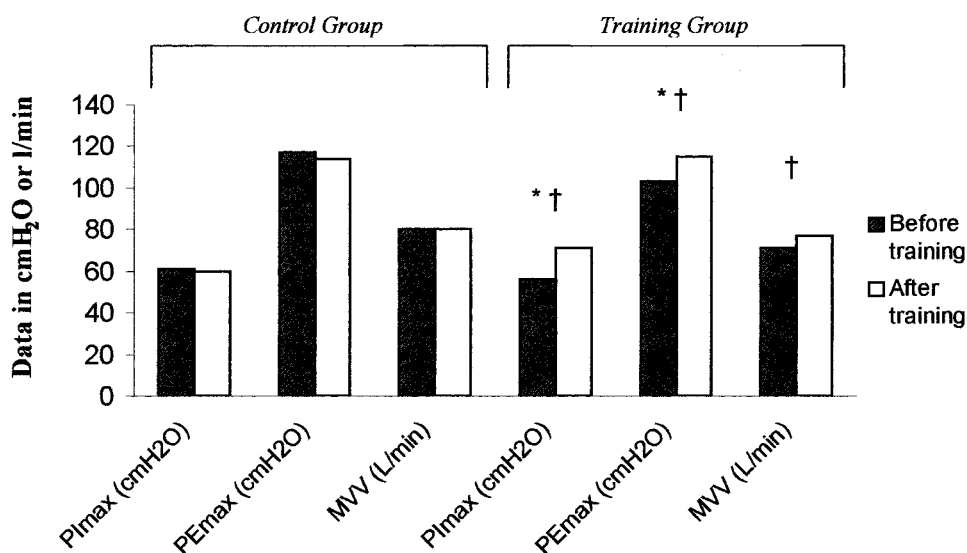


FIGURE 1. Respiratory strengths and endurance. \*p < 0.05 for both groups compared to baseline values; †p < 0.05 for the training group compared to its baseline value.

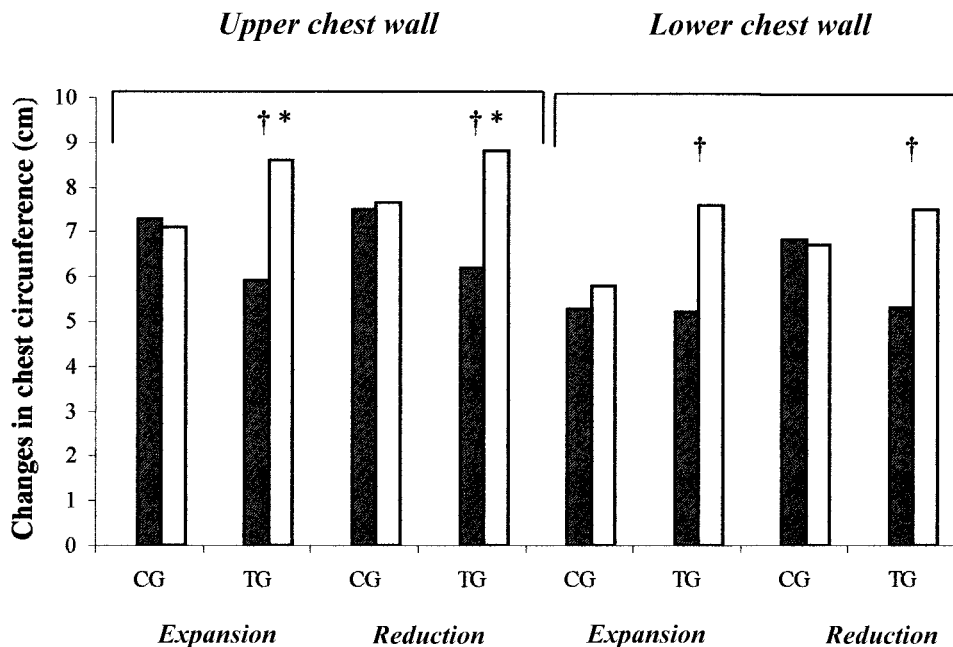


FIGURE 2. Upper and lower chest wall mobility expansion and reduction in the control group (CG) and training group (TG). \* $p < 0.05$  for both groups compared to baseline values; † $p < 0.05$  for the training group compared to its baseline value.

respect to the control group or in comparison to baseline values. Results are shown in Figure 2.

### HRQL

After 8 weeks, changes in one of the nine short form-36 domains (role physical) showed a significant improvement in training group ( $50 \pm 43$  to  $71 \pm 43$ ,  $p = 0.01$ ) compared to the control group. Physical function and role emotional domains improved ( $59 \pm 26$  to  $64 \pm 23$  and  $88 \pm 36$  to  $100$ , respectively) in the training group, but no significance was found with respect to the control group or compared to its baseline values. In the control group, bodily pain domain improved from  $75 \pm 26$  to  $85 \pm 23$ , but this was not significant compared to the training group or its baseline values. All other domains were unchanged after 8 weeks.

### DISCUSSION

Our study results are consistent with previous studies<sup>20,21</sup> in patients with generalized MG. We found that an IMT program using the interval-based technique added to BR leads to an increase in respiratory strength and endurance,  $\dot{V}_E$ ,  $V_T$ ,  $TTOT$ , and upper chest wall mobility, and a decrease in the RR and  $V_T/RR$  ratio.

To our knowledge, this is the first randomized controlled trial of inspiratory IMT applied in MG

patients. The interval-based training technique was normally applied with repeated series of high loads separated by recovery periods so as to maximize magnitude of the training in the peripheral skeletal muscle,<sup>22–25</sup> as in respiratory muscle.<sup>26–28</sup> Due to the tendency of muscles to fatigue quickly with repetitive exercise in MG, we decided to evaluate the viability and benefits of this interval-based training method.

The mean increase in the  $P_{1max}$  after the 8-week program was 27%. The load applied at the onset of the program was very low (20% of  $P_{1max}$ ) and was increased over the 8 weeks to a moderate load (60% of  $P_{1max}$ ). As loads did not exceed 70% of  $P_{1max}$  over the 8 weeks, the expected result of training would be improved muscle endurance. The characteristics of our program are based on low-intensity loads applied at high rates in the first 3 weeks, low-to-moderate-intensity loads applied with moderate rates in weeks 3 to 6, and moderate intensity loads applied with low rates in the last 2 weeks. The mixed aerobic/anaerobic training in relation to intensity and frequency favored an improvement in strength rather than in respiratory muscle endurance.

Respiratory muscle training has been applied previously in MG in only two studies,<sup>20,21</sup> both of which were nonrandomized. Gross and Meiner<sup>20</sup> were the first to use respiratory muscular training in this setting, but they used resistive breathing throughout

the respiratory cycle. Although they demonstrated increases of 70% in P<sub>imax</sub> and 44% in MVV, results significantly higher than ours, their patients showed intense weakness of inspiratory muscles at baseline. Besides, their training program was longer and more intense than ours; it consisted of 12 weeks of training with 10 min three times daily on the threshold of fatigue. Training was done with a different type of valve that depended on the generated flow to be effective. As it was not therefore possible to impose P<sub>imax</sub>-related loads, the training program is difficult to reproduce. The results of Weiner et al<sup>21</sup> were similar to ours, although their training group included patients with greater muscular weakness than our group. P<sub>imax</sub> increased in their patients between 53% and 57%. The device used was the same as ours, and the program was similar to that of our study. Like Gross and Meiner,<sup>20</sup> Weiner et al<sup>21</sup> also continued their study for 12 weeks, with a greater total time of training, and greater intensity. The aim of our study did not include daily training because we consider it inappropriate for MG pathophysiology. Repeated exercise may cause a loss of K<sup>+</sup> ions from contracting muscle<sup>38</sup> and a decrease in the gradient regulated by muscle Na<sup>+</sup> - K<sup>+</sup>-adenotriphosphatase has been related to muscular fatigue.<sup>39</sup> Furthermore, the K<sup>+</sup> homeostasis in exercising has been connected with recovery time duration.<sup>40</sup>

Another important finding in our study was the substantial increase in P<sub>emax</sub>. Our program was not directly targeted to expiratory muscles, although an improvement in respiratory mechanics is associated with PLB.<sup>41</sup> PLB provides expiratory resistance of 2 to 4 cm H<sub>2</sub>O,<sup>42</sup> and this could have influenced the functional improvement of these muscles. To our knowledge, no other studies have found P<sub>emax</sub> increases without the direct application of training on these muscles.

Compliance with our partial home program was satisfactory. We believe that programs of this type should be designed for future use in MG and other neuromuscular diseases, as they may be easily incorporated into daily routines helping to maintain respiratory muscle strength and healthy respiratory mechanics.

Our study is limited by the sample size of patients with generalized MG, but these patients represent 50 to 70% of the total group of MG patients.<sup>33</sup> Another limitation of this study may be the relative accuracy of the thoracic mobility outcome. Nevertheless, although the thoracic mobility values showed high intersubject variability, the program applied clearly demonstrated that rib cage mobility improved with the application of our protocol.

In summary, since no changes in severity of MG disease were seen, it can be concluded that simple

partial home interval-based IMT combined with BR in patients with generalized MG leads to notable improvements in respiratory muscle strength, chest wall mobility, respiratory pattern, and in respiratory muscle endurance, but does not appear to improve lung function.

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Guilherme Augusto de Freitas Fregonezi, Vanessa Regiane Resqueti, Rosa Güell, Jesus Pradas and Pere Casan

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