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Effect of the Respiratory Muscle Training on Lung Function and Respiratory Muscle Strength in Patients with Moderate Myasthenia Gravis: A Meta-Analysis and Systematic Review

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Abstract

Background: Respiratory muscle impairment is common in patients with moderate Myasthenia Gravis. Whether respiratory muscle training (RMT) improve lung function tests and/or respiratory muscle strength is still debatable.

Methods: A systematic review and a meta-analysis including the relevant randomized controlled trials (RCTs) and prospective studies published from June 1996 and June 2016 and assessing the effect of the (RMT) on the respiratory muscle tests and the respiratory muscle strength.

Results: One RCT and 2 prospective cohort studies were included. Respiratory muscle training was found to improve the Maximal voluntary ventilation (MD=-10.3 L/min; CI95% [-17.95, -2.31]; p=0.01; I²=0%; n=24). However, it improved neither FEV1 (MD=-0.10 L; CI95% [-0.28, 0.08]; p=0.27; I²=0%; n=24) nor the Vital Capacity (MD=-0.06; CI95% [-0.24, 0.13]; p=0.57; I²=0%; n=24).

Respiratory muscle training did not significantly improve the Maximal inspiratory pressure (PImax) (MD=-15.35; CI95% [-38.5, 7.8]; I²=97%; n=34). However, it significantly improved the maximal expiratory pressure (PEmax) (MD=-14.7; CI95% [-18.3, -11.12]; p<0.001; I²=51%; n=24).

Conclusion: The respiratory muscle training significantly improves the maximal voluntary ventilation and the maximal expiratory pressure. Further studies with larger sample size are required to confirm these findings.

Keywords: Myasthenia gravis; Physical endurance; Respiratory function tests; Respiratory muscles

Introduction

Myasthenia Gravis (MG) is a rare autoimmune disease affecting the neuromuscular junction [1,2]. Its prevalence has been reported to be increasing worldwide, ranging from 60 to 200 cases per million populations [3-5]. Muscle weakness and fatigue are the clinical hallmark of the disease, typically increasing with exercises and improving with rest [5,6]. Myasthenic crisis is the most serious complication, affecting 20 to 30% of patients with MG [7,8]. Its seriousness is mainly related to an acute impairment of the respiratory and/or the upper airway muscles, usually requiring mechanical ventilation assistance [7,8]. In patients with stable moderate MG, respiratory muscle weakness may lead to decreased vital capacity and deteriorated cough and sigh [9,10]. As a result, these patients are at high risk of atelectasis, chest infection and impaired oxygenation. Whether respiratory muscle training in patients with moderate MG is beneficial for the lung function and whether it can enhance their strength is still debatable, relaying on few trials with limited sample size [11-14].

In the current meta-analysis, we aimed to systematically review all the published randomized controlled trials (RCTs) and prospective studies assessing the impact of respiratory muscle training on the lung function tests and the respiratory muscle strength.

Materials and Method

Search strategy

A systematic search of the relevant RCTs and prospective studies published from June 1996 and June 2016 was conducted in Pubmed and Cochrane library database by two trained investigators (AC and KH). The following MeSH and keywords were used: Myasthenia Gravis, Physical endurance, respiratory function tests, respiratory muscles. Different Boolean combination using the connectors AND/OR were

performed. References of the identified studies were also reviewed for possible inclusion. Only RCTs and prospective studies published in English were considered for this systematic review.

Study selection and quality assessment

Titles, abstracts and references of all the articles reviewed in the first screening were reviewed by both investigators to check the inclusion and exclusion criteria. Inclusion criteria were the following: (1) all the included patients were labeled as having stable and generalized MG (Osserman-Genkins classification II or III). (2) Intervention: respiratory muscle training with a pre and post training assessment of the lung function tests, and the strength of the respiratory muscle. The latter is evaluated by the measurement of the maximal inspiratory and expiratory pressures. (3) Outcome: Improvement ore deterioration of the lung function tests and/or of the respiratory muscle strength.

We excluded from this meta-analysis: (1) retrospective studies, (2) studies including patients on mechanical ventilation or having myasthenic crisis, (3) studies involving patients who were already

included in previous prospective studies or RCTs eligible for the current meta-analysis, (4) studies with confounding factors (different medical management strategies, variable training protocols within the same study, perioperative period of thymectomy).

The quality of the included studies was assessed by JADAD score for RCTs [15] and by Newcastle - Ottawa quality assessment [16].

Data extraction and study characteristics

We extracted the study design, the modality and the period of respiratory muscle training. All the included studies must include the
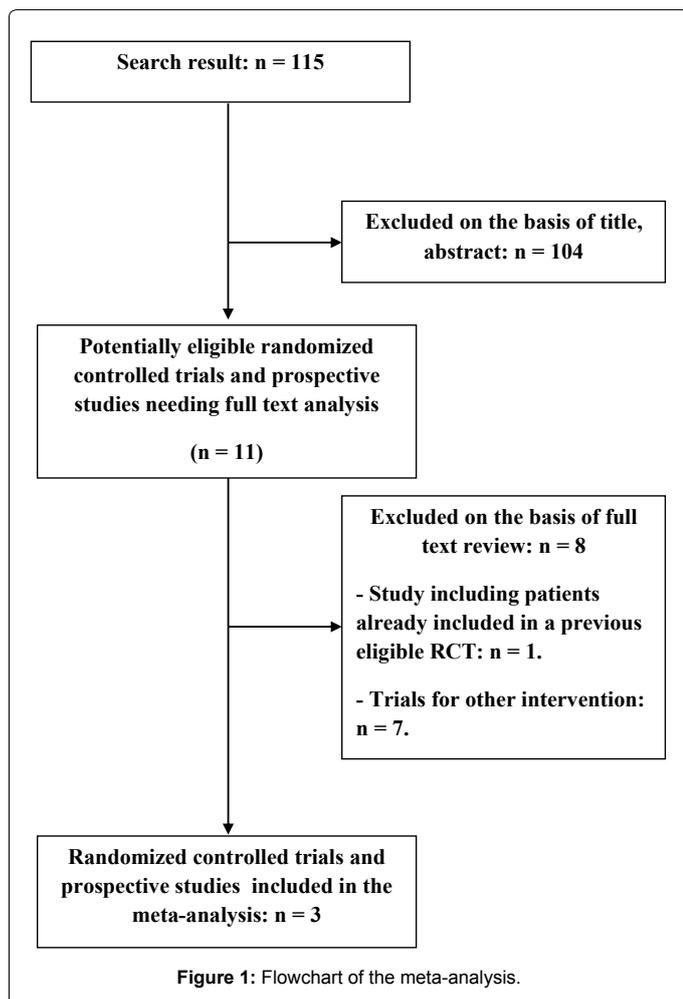
required data regarding the lung function tests (Maximal voluntary ventilation (MVV), Forced expiratory ventilation (FEV1) and vital capacity (VC)), the maximal inspiratory pressure (PImax) and the maximal expiratory pressure (PEmax) before and after the training.

Statistical analysis

The lung tests parameters, PImax and PEmax were compared before and after respiratory muscle training. Data were extracted as continuous variables and entered as mean ± standard deviation (SD). Secondly, these data were pooled to calculate the inverse variance mean difference (MD) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed by the Q test and the I^2 test [17]. I^2>25%, 50% and 75% was respectively considered as reflecting mild, moderate and severe heterogeneity. Accordingly, Fixed-effect model or random-effect model were chosen [17]. Forrest plots were also constructed. A p value<0.05 for Q test and <0.1 for I^2 test were considered as statistically significant. The statistical analysis was performed using RevMan 5.3 according to Cochrane collaboration and the Quality of reporting meta-analysis recommendations [18].

Results

Study characteristics

One hundred fifteen studies were identified after the initial search. One hundred four studies were excluded after the first screening and 11 studies were thoroughly reviewed. Finally, only three studies (34 patients) met the inclusion/exclusion criteria and were included in the meta-analysis [11-13]. The flowchart of the study is shown in Figure 1.

Only the group of patients who had respiratory muscle training was included in the current meta-analysis. Among the included studies only one was a randomized controlled trial comparing a training group to a control group [11]. After assessing the quality criteria, JADAD score was 3 for this RCT. The two remaining studies were nonrandomized controlled trials. Both had a Newcastle-Ottawa score of 6 stars. The characteristics of the included studies are shown in Table 1.

Effect of respiratory training on lungs function tests

Data regarding the lungs function tests were available in two included studies [11,12]. After pooling the results of these two studies, respiratory muscle training was found to improve the MVV (MD=-10.3 L/min; CI95% [-17.95, -2.31]; p=0.01; I^2=0%; n=24). However, respiratory muscle training improved neither FEV1 (MD=-0.10 L; CI95% [-0.28, 0.08]; p=0.27; I^2=0%; n=24) nor the VC (MD=-0.06; CI95% [-0.24, 0.13]; p=0.57; I^2=0%; n=24) (Figure 2).

Effect of respiratory training on respiratory muscle strength

Data regarding the effect of respiratory muscle training on the

Figure 1: Flowchart of the meta-analysis.

First author	Year	Design	No. patients with moderate MG	No patients with respiratory training	Osserman and Genkins classification	Exercise modality
Rassler [12]	2007	Prospective cohort study	10	10	IIa, IIb	- Normocapnic hyperpnea using a training device. - 30 min per session/Total of 20 sessions. - Respiratory training period: 4-6 weeks.
Fregonezi [11]	2005	RCT	27	14	IIa - IIb	- Interval-based inspiratory muscle training. - Combination of DB and PLB. - 45 min per session/3 sessions per week. - Respiratory training period: 8 weeks.
Weiner [13]	1998	Prospective cohort study	10	10	IIa, IIb, III	- Inspiratory and expiratory muscle training. - Training by using a two-way Hans-Rudolph Valve. - 30 min per session/6 sessions per week. - Respiratory training period: 3 months.

RCT: Randomized Controlled Trial; DB: Diaphragmatic Breathing; Pursed-Lips Breathing

**Table 1:** Characteristics of the studies included in the meta-analysis.
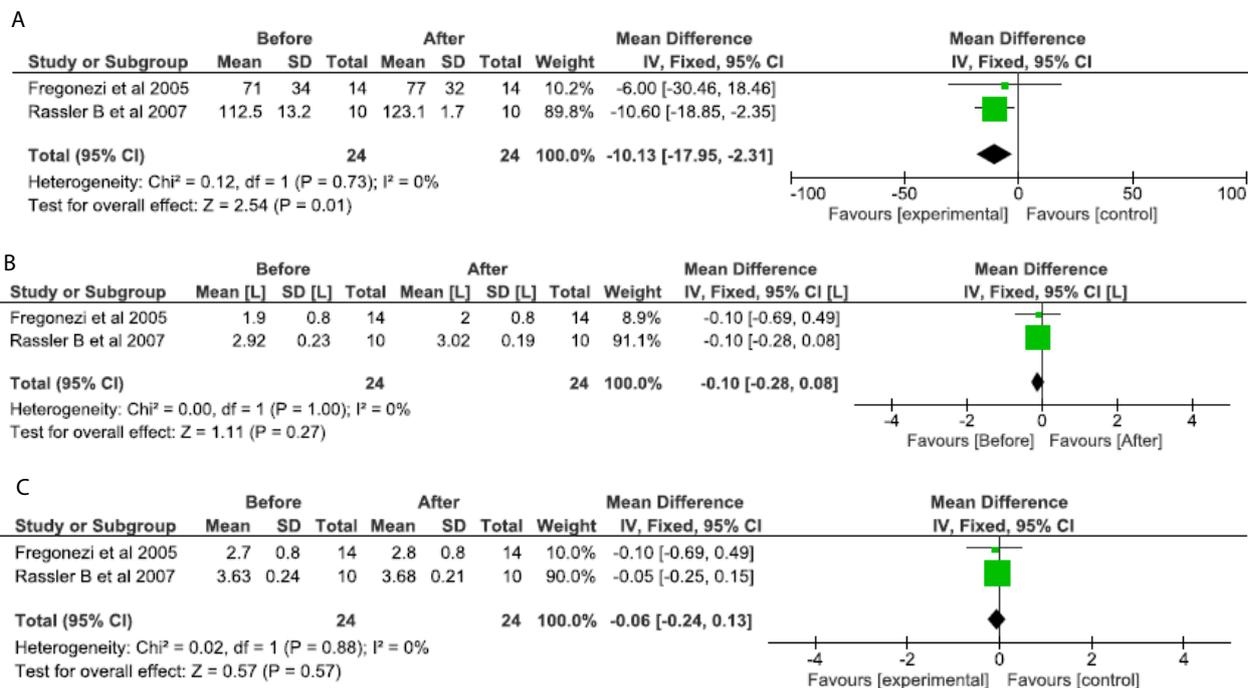
Figure 2: Effect of respiratory muscle training on lung function tests (A: Maximal Voluntary ventilation, B: Forced expiratory volume 1. C: Vital capacity).
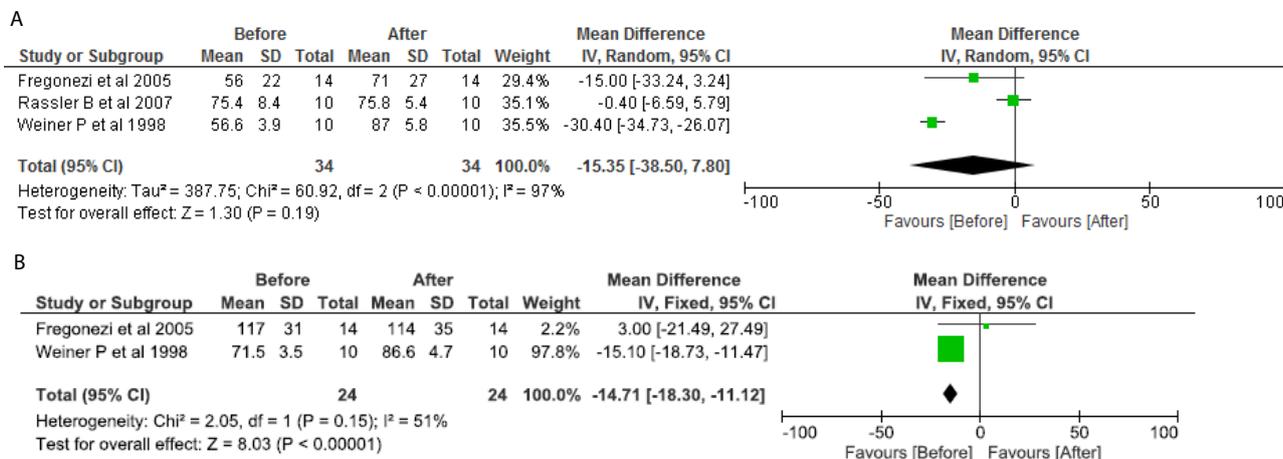

Figure 3: Effect of respiratory muscle training on respiratory muscle strength (A: Maximal Inspiratory pressure (PImax), B: Maximal expiratory pressure (PEmax)).

maximal inspiratory pressure were available in all the included studies [11-13]. Respiratory muscle training did not significantly improve the PImax (MD=-15.35; CI95% [-38.5, 7.8]; n=34). However, significant heterogeneity was noticed between the included studies as I^2 was 97%.

Data regarding the effect of respiratory muscle training on the maximal expiratory pressure were available in two included studies [11,13]. Unlike PImax, the respiratory muscle training significantly improved the PEmax (MD=-14.7; CI95% [-18.3, -11.12]; p<0.001; I^2=51%; n=24) (Figure 3).

Discussion

The main finding in the current meta-analysis is that the respiratory muscle training significantly improved the lung function by increasing the maximal voluntary ventilation. Similarly, it is beneficial for the respiratory muscle strength as it significantly increased the maximal expiratory pressure.

Preventing respiratory muscle dysfunction is challenging in patients with Myasthenia Gravis. In patients with mild to moderate stable generalized MG, respiratory dysfunction may progressively lead to microatelectasis, pneumonia and increased ventilation load [19,20]. This respiratory dysfunction is mainly related to the weakness of the inspiratory muscle rather than impaired neural drive. In fact, it has been reported that patients with stable MG had decreased respiratory strength and endurance when compared to healthy population [11,21].

In a prospective study including 17 patients with MG, Keenan et al. [21] reported that PImax was decreased to 70% and PEmax was decreased to 50% of the predicted values. On the other hand, Baydur et al. [20] reported that the neural drive, assessed by the measurement of the P0.1 is even increased in this group of patients which enable them to preserve normal gas exchanges and to escape from hypercarbia. Hence, respiratory muscle training may improve lung functions test and respiratory muscle strength and may reduce the overstimulation of the neural respiratory drive. The benefit of respiratory muscle exercises was even reported in patients with severe MG requiring intubation and mechanical ventilation. In fact, Varelas et al. [9] reported in a retrospective study including 18 MG ventilated patients that chest physiotherapy associated to intermittent positive pressure breathing sigh and bronchodilators significantly reduced the long-term complications related to mechanical ventilation.

Despite these findings suggesting that respiratory muscle training can be a therapeutic option to improve respiratory muscle strength, only limited studies were conducted in this regard [11-14]. This can be explained by the clinical characteristics of the disease itself as the muscle weakness in patients with MG is alleviated by rest and enhances by increased work [22-24].

Our results show that respiratory muscle training significantly improved the maximal voluntary ventilation. This parameter was previously used to assess the ventilatory muscle endurance [25]. In fact, it represents the maximal volume that can be voluntarily mobilized into and out of the lung during 10 to 15 seconds interval [26]. This parameter is also helpful as a follow-up tool in patients with MG as it enables early diagnosis of respiratory muscle impairment in patients with MG. In fact, Heliopoulos et al. [27] reported that MVV is preserved in patients with grade (I) MG according to Osserman classification whereas decremental MVV decrease can be seen in patients with grade (IIa) or (IIb) even in asymptomatic patients. However, MVV is highly affected by the respiratory flow which may limit its usefulness in patients with parenchymal lung or airflow limitation diseases [21]. Unlike MVV, the other lung tests were not significantly improved by the respiratory muscle training. In fact, FEV1 and VC are static tests with a constant respiratory load of work. Thus, the physiopathology and the clinical characteristics of MG may explain the deficiency of these tests to identify any benefit from the respiratory muscle training on the ventilation.

The second finding of the current meta-analysis is that respiratory muscle training significantly improved the PEmax. In fact, expiration is a passive phenomenon in healthy people. However, in patients with respiratory insufficiency, the accessory expiratory muscles are of paramount importance. Hence, we postulate that in patients with myasthenia gravis, the improvement of the PEmax was mainly related to the improvement of the expiratory muscle function after the training period [12]. On the other hand, the current meta-analysis failed to show any benefit of the respiratory muscle training on the PImax. This conclusion should be taken with caution as a significant heterogeneity between the included studies was found.

Even though the current meta-analysis is the first to assess the effect of respiratory muscle training on lung function tests and respiratory muscle strength, several limitation should be mentioned. First, all the three studies had a limited sample size. In fact, even after pooling the results of all these studies, only 34 patients were included. Second, the training protocols were different even though they were well standardized in each study. Finally, the medical management and the co-morbidities of the included patients were not mentioned in most of the studies.

Conclusion

The respiratory muscle training significantly improves the maximal voluntary ventilation and the maximal expiratory pressure. Further studies with larger sample size are required to confirm these findings.

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