

Pulmonary function and respiratory muscle strength in myasthenia gravis.

Função pulmonar e força muscular ventilatória em Miastenia Gravis.

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Abstract

Introduction: Myasthenia gravis (MG) is a neuromuscular autoimmune disease of unknown etiology, characterized by generalized muscle weakness and fatigue, especially after repetitive physical activities, with consequent improvement after rest. The MG follows a slowly progressive course, which can be fatal failure of the ventilatory muscles. The manifestations of the respiratory system are generally attributed to the weakness of the diaphragm and also accessory muscles of ventilation. **Objetive:** The objective was to evaluate the volumes and lung capacities and maximum pressure ventilation in patients with clinically stable MG. **Methods:** This is an observational study involving 15 patients (2 men) with MG. Subjects were recruited consecutively and screened for eligibility using the standardized protocol. **Results:** Spirometry, only two patients showed abnormalities of respiratory pattern, being a moderate restrictive pattern (50-60% predicted), and another patient with the congenital form showed a severe restrictive pattern. Not obstructive patterns were observed. Our results of spirometry showed an average value of FVC: 3.15 ± 0.77 and FEV1: 2.64 ± 0.65 . Regarding the maximum pressure generated by the ventilatory muscles, the average value for the MIP was 45.5 cmH₂O among women and the value of 56 cmH₂O for men was observed. To MEP it was observed the average value of 45 cmH₂O for women and 55 cmH₂O for men. **Conclusion:** We conclude that patients with MG have lower values of maximal inspiratory and expiratory ventilatory associated with normal lung function values.

Key Words: Myasthenia Gravis, spirometry, maximal ventilatory pressures.

Resumo

Introdução: A Miastenia gravis (MG) é uma doença neuromuscular auto-imune de etiologia desconhecida, caracterizada por fraqueza generalizada e fadiga muscular, especialmente após atividades físicas repetitivas, com consequente melhora após o repouso. A MG segue um curso progressivo lento, que pode ser fatal a falência dos músculos ventilatórios. As manifestações no sistema respiratório geralmente são atribuídas à fraqueza do músculo diafragma e de mais músculos acessórios da ventilação. **Objetivo:** O objetivo foi avaliar os volumes e capacidades pulmonares e as pressões máximas ventilatórias em pacientes com MG clinicamente estáveis. **Método:** Trata-se de um estudo observacional envolvendo 15 pacientes (2 homens) com MG. Os sujeitos foram recrutados consecutivamente e avaliados para elegibilidade de acordo com o protocolo padronizado descrito abaixo. **Resultados:** Na espirometria, apenas dois pacientes apresentaram alteração do padrão ventilatório, sendo um padrão restritivo moderado (50 a 60% do previsito) e outro paciente, com a forma congênita apresentou um padrão restritivo grave. Não foram observados padrões ventilatórios obstrutivos. Nossos resultados da espirometria mostraram um valor médio para a CVF de $3,15 \pm 0,77$ e VEF1 de $2,64 \pm 0,65$. Em relação a pressão máxima gerada pelos músculos ventilatórios, foi observado o valor médio para a PImax de 45,5 cmH₂O entre as mulheres e o valor de 56 cmH₂O para os homens. Para a Pemax observamos o valor médio de 45 cmH₂O para as mulheres e 55 cmH₂O para os homens. **Conclusão:** Podemos concluir que pacientes com MG apresentam valores reduzidos de pressões máximas ventilatórias inspiratórias e expiratórias associado a valores normais de função pulmonar.

Palavras-Chave: Miastenia gravis, espirometria, pressões ventilatórias máximas.

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INTRODUCTION

Myasthenia gravis (MG) is a neuromuscular autoimmune disorder of unknown etiology disease is characterized by generalized muscle weakness and fatigue, especially after repetitive physical activities and consequent improvement after rest. Their severity depends on the amount of muscle groups involved, ranging from mild cases with ocular symptoms to severe cases with generalized muscle weakness including respiratory failure.⁽¹⁻³⁾ These symptoms are more common in generalized form.⁽⁴⁾

According to the classification Osserman and Gerkins, MG was initially divided into groups I, II-A and II-B, III and IV and the appearance of symptoms and disease severity. Approximately 70% of patients are classified in groups IIa and IIb. In early disease, impairment of the respiratory muscles is observed in only 1-4% of patients, however, in the later stages it reaches 60-80% of these.^(5,6) Patients usually report dyspnea due to muscle weakness, starting with great efforts and reaching resting dyspnea.

The MG follows a slowly progressive course, which can be fatal when ventilatory muscles fail. The manifestations of the respiratory system are generally attributed to the weakness of the diaphragm and other accessory muscles of ventilation.⁽⁷⁾ The progressive ventilatory muscle wasting begins to produce a ventilatory change, initially the "restrictive" pattern, with respiratory failure due to hypoventilation.⁽⁸⁾ in recent years, several authors have analyzed lung function in patients with MG.⁽⁹⁻¹¹⁾ the purpose of this study was to evaluate the volume and lung capacity and maximal ventilatory pressures in patients with MG.

METHOD

This is an observational study involving patients with MG. According to the established protocol, evaluations were performed at the Sleep Laboratory of Master's and PhD Degree Pos Graduation Programs in Rehabilitation Sciences, Universidade Nove de Julho - UNINOVE. The design, Conduction, and reporting of this study will follow the norms of the The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies (Figure 1).

Ethical considerations

The study was be conducted in accordance with the ethical standards established in the 1961 Declaration of Helsinki (as revised in Hong Kong in 1989 and Edinburgh, Scotland, in 2000) and is in compliance with the Regulatory Guidelines and Norms for Research Involving Human Subjects of the National Health Board of the Brazilian Health Ministry issued in December 2012.

This study received approval from the Human Re-

search Ethics Committee of Universidade Nove de Julho (Brazil) under process no. 360.488 and is registered with the World Health Organization (WHO) under Universal Trial Number (UTN) U1111-1147-7853 and the Brazilian Registry of Clinical Trials (REBEC) RBR-7ckpdd. A signature of informed consent will be required, and subjects were being allowed to withdraw from the study at any time with no negative consequences. All procedures this study was be of personal, confidential nature, subject to therapist/patient confidentiality.

Subjects

Subjects with MG were recruited prospectively from the Setor de Investigação de Doenças Neuromusculares da Universidade Federal de São Paulo and sent to the Sleep Laboratory of the Universidade Nove de Julho, São Paulo (Brazil). Participants were be recruited consecutively and screened for eligibility using a standardised protocol. The eligibility criteria are described below. Inclusion criteria comprise 18–65-year-old patients of both sexes diagnosed with clinically stable MG, who agree to participate in this study by signing the informed consent. The study was exclude subjects with any of the following: ischemic and dilated heart disease; episodes of acute decompensation in the two months prior to the study protocol; primary heart valve disease; acute or chronic cardiopulmonary or neuromuscular diseases; history of recent surgical procedures in the thoracic region; history of stroke; mental instability; drug use; and alcohol abuse.

Clinical Evaluation

All procedures were explained. Those patients who agreed to participate in the study underwent a detailed evaluation containing disease history, physical examination, which involved the measurement of blood pressure, heart and respiratory rates. All participants underwent evaluation protocol described below. Data acquisition and interpretation of the index tests and reference standards was composed by researchers blind (masked) to the results and other clinical information.

LUNG FUNCTION TESTS

Spirometry

Spirometry was performed according to the recommendations by the ATS/ERS task force for standardization of lung function testing,⁽¹²⁾ and national guidelines for the execution of lung function tests, calibration and equipment maintenance by the Sociedade Brasileira de Pneumologia e Tisiologia.⁽¹³⁾

The pulmonary function test was done during the day, seated in a comfortable position, with the body erect and the upper limbs unsupported, on a flow spirometer KoKo® PFT Spirometer System Version 4.11

(nSpire™ Health, Inc., Louisville, CO, USA). Post-bronchodilator spirometry was performed after two puffs of salbutamol (400 µg) administered with a Spacer (Volumantic; GlaxoSmithKline®) in all patients with airway obstruction at baseline. All examinations will be carried out by a competent technician trained in obtaining the necessary cooperation from the subjects and appropriately operating the equipment in order to ensure accurate, reproducible results.

For analysis, the best forced expiratory volume after first second (FEV1) and forced vital capacity (FVC) were chosen regardless of the curve. The 'best test' curve was selected from the largest sum of FEV1 and FVC. All other lung function parameters selected for analysis were taken from the 'best test' curve. The equipment will be calibrated prior to each exam with a 3 L syringe. ATS/ERS acceptability criteria for spirometric testing were applied, including a minimum of three respiratory manoeuvres with at least two free from artefacts. Furthermore, respiratory manoeuvres were required to show a back-extrapolated volume\5% of FVC and to meet ATS/ERS "end of test" criteria. Reproducibility criteria included a difference between the best and second best values for FVC and FEV1\200 ml. Diagnosis of restriction was based on an FVC below the age- and gender-adjusted predicted lower limit of normal (LLN) for FVC as defined by the ATS/ERS.⁽¹⁴⁾

Definition of airway obstruction

ATS/ERS criteria served as "reference standard" for detection of airway obstruction.⁽¹²⁾ The LLN was defined as age- and gender-specific fifth percentile of a healthy never-smoking population. Reference equations derived from the National Health and Nutrition Examination Study (NHANES) III were used to calculate predicted values and LLN. Individuals above or below the fifth percentile were identified as normal and abnormal, respectively. Additionally, airway obstruction was calculated using the GOLD criteria (FEV1/ FVC\70%).

Subjects identified as normal by both cutoffs were categorized as true negatives, subjects identified abnormal by both cutoffs as true positives, subjects with an FEV1/ FVC\LLN but with FEV1/ FVC 70% as false negatives and subjects with an FEV1/ FVC the fifth percentile but FEV1/ FVC ratio\70% as false positives, respectively. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value for GOLD criteria were calculated with ATS/ERS criteria (FEV1/FVC\LLN) serving as "reference standard."⁽¹⁵⁾

Analysis of ventilatory muscle strength

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) constitute the most physiologically adequate tests for the determination of ventilator muscle strength. MIP is an indicator of ventilator capaci-

ty and the development of respiratory failure and is indicated for assessing the degree of abnormality and monitoring the weakening of inspiratory muscles individually in the progress of the disease.⁽¹⁶⁾ The tests were performed in a quiet setting on the same day on which the patients undergo spirometry.

The patients will be seated comfortably, with the trunk at a 90-degree angle in relation to the thighs and breathing calmly and at rest, using a nose clip. We will use two manovacuometers, an analogical aneroid RECORD (GER-AR® Comércio Produtos Médicos Ltda, São Paulo, Brazil) and another digital model, the MVD300 (Globalmed® Porto Alegre, RS, Brazil) with a pressure transducer and operating range of 0 ± 300 cm H2O. As recommended, we will use a nozzle adapter equipped with an orifice of approximately 2 mm in diameter and 15 mm in length in order to provide an air leak and thus prevent the increase of pressure in the oral cavity generated by the undesired contraction of the muscles of the buccal wall, thereby avoiding interference in the results.⁽¹⁷⁾

The digital manometer is connected to MVD300 software installed on a computer that allows viewing of graphs of sustained ventilatory muscle strength during the performance of manoeuvres effort. The MIP will be measured from the residual volume (RV), requesting a maximum inspiration from a maximal expiration, while the MEP will be verified from the total lung capacity (TLC), after the individual performs a maximal inspiration.

All individuals carry out at least three reproducible manoeuvres on each of the devices supported by at least one second on analogical equipment and four seconds on digital equipment to observe the support of respiratory muscle strength. Data analysis will be computed as the value of the largest analogical, provided this does not exceed 10% over the nearest; in digital, we adopted the same procedure to register the value provided by the device (peak value), as well as the first, second, third, and fourth seconds of support obtained by extrapolating the numerical charts provided by the equipment.⁽¹⁸⁾

RESULTS

The study included 15 patients (13 females) with clinically stable MG. Anthropometric and demographic characteristics are described in Table 1.

Table 1. Anthropometric and demographic characteristics

Variables	(n=15)
Age (anos)	41±11,32
Weight (kg)	78±15,27
Height (cm)	163±7,76
IMC (kg/m ²)	29,34±5,30

Note: BMI – Body Mass Index

The absolute spirometric values and maximum ventilatory pressures (MIP and MEP) are presented in table 2 and 3.

In Figure 2 we can see the results of the correlation between the values of forced vital capacity and maximal ventilatory pressures.

Subtitle: FVC: forced vital capacity; MIP: Maximal Inspiratory Pressure; MEP: Maximal expiratory pressure.

DISCUSSION

A MG is the most common primary neuromuscular transmission disease. It is characterized by skeletal muscle weakness and fatigue that can variously involve respiratory muscles. It is important to assess the level of impaired respiratory function at all stages of the disease, since 90% of the patients develop a generalized form⁽¹⁹⁾, and of these, between 30% and 40% go on to develop respiratory complications.⁽²⁰⁾

Most MG patients have weakness and muscle fatigue, especially in generalized cases. This framework of progressive muscular involvement will generate a ventilatory change, initially restrictive character, with the installation of respiratory failure due to hypoventilation. Regarding lung function, patients with MG often have a "myasthenic pattern" characterized by reduced ventilatory muscle endurance and reduced volumes.^(21, 22) This ventilatory muscle impairment will interfere with the performance of physical activities and daily lives of patients.

Spirometric results correlate with scientifically-morbidity and life expectancy, revealing the general health under cardiopulmonary aspect. Spirometry is recommended in clinical practice pulmonology as a sup-

plementary means when deciding the severity of the disease and therapeutic indication. Therefore, assessment of respiratory function and inspiratory and expiratory muscle strength are extremely important and useful in order to monitor disease progression and prevent iden-

Table 3. Maximum ventilatory pressure

Variable	MIP	MEP
LC	50	50
JCG	52	40
SCF	65	120
EFS	60	60
PCF	46	42
MO	56	60
JB	30	50
TSR	52	40
MJS	36	24
ASC	52	16
MHA	20	16
MFS	24	8
MCS	50	60
KO	50	40
ADF	60	70
Média	46,97±13,43	46,4±27,41
Predicted		
- Men		
40-49 years	115.8 ± 87.0*	126.3 ± 18.0*
- Women 40-49 years	87.0 ± 9.1	85.4 ± 13.6

Note: MIP – Maximum inspiratory pressure; MEP – Maximum expiratory pressure.

Table 2. Absolut spirometry data.

	FVC pred.	FVC Obt.	FVC % of pred.	FEV ₁ Pred.	FEV ₁ obt.	FEV ₁ % of pred.	FEV ₁ /FVC Pred.	FEV ₁ /FVC Obt.	FEV ₁ /FVC % of pred.
LC	3.32	2.95	89%	2.7	2.47	91%	0.81	0.84	104
JCG	5.06	2.09	41%	4.3	1.51	35%	0.86	0.72	84
SCF	4.53	3.86	85%	3.78	3.15	83%	0.83	0.82	98
EFS	3.75	3.84	102%	3.18	3.26	102%	0.85	0.85	100%
PCF	3.50	3.57	102%	2.9	3.01	104%	0.82	0.84	102
MO	2.72	2.99	110%	2.23	2.52	113%	0.81	0.84	104
JB	3.07	2.64	86%	2.66	2.15	81%	0.85	0.81	95
TSR	3.29	3.35	102%	2.99	3.26	109%	0.94	0.97	104
MJS	3.66	3.03	83%	3.02	2.63	87%	0.82	0.87	106
ASC	3.33	2.67	80%	2.9	2.29	79%	0.87	0.86	98
MHA	4.11	3.56	87%	3.51	2.78	79%	0.87	0.78	90
MFS	2.76	1.56	57%	2.23	1.28	57%	0.8	0.82	102
MCS	3.14	3.47	110%	2.58	2.93	114%	0.81	0.84	104
KO	3.26	2.94	90%	2.72	2.62	96%	0.83	0.89	108
ADF	4.56	4.75	104%	3.76	3.73	99%	0.82	0.79	96

Note - FVC – Forced Vital Capacity; FEV₁ - forced expiratory volume after first second.

tify early changes in ventilation perfusion.

The first document of the American Thoracic Society (ATS) on standardization of spirometry was published twenty-two years based on the Snowbird Workshop held in 1979 in the United States. The initial document was updated in March 1987, after eight years of clinical experience with the use of initial recommendations.

The continuous progress of science and the increasing use of spirometry as a diagnostic tool in clinical practice, especially with the chronic obstructive pulmonary diseases associated with the use of the computer in calculating the values for the test generated a need for revision of the old recommendations. So in 1994, the American Thoracic Society, aiming to improve the way of execution and reduce the variability of interpretation issued new guideline as a standard for spirometry.

Spirometry is a medical test that quantifies the volume of air that a person inspired or expired due to the variable time. By spirometry can also evaluate the flow, that is, the speed, that the volume of air that move as a function of time within the airways. It allows the determination of static lung volumes (total lung capacity - TLC, functional residual capacity - FRC, residual volume - VR) and dynamic values (slow vital capacity - VC, forced vital capacity - FVC, forced expiratory flow in one

second - FEV₁) and derivatives thereof.^(12, 13)

In this study, of the fifteen patients who underwent pulmonary function tests, 02 were type of congenital MG, one ocular MG and the other had the generalized form. Spirometry, only two patients showed abnormalities of respiratory pattern, being a moderate restrictive pattern (50-60% predicted), and another patient with the congenital form showed a severe restrictive pattern. Not obstructive patterns were observed. Our results of spirometry showed an average value of FVC: 3.15 ± 0.77 and FEV₁: 2.64 ± 0.65.

In the study of Fregonesi et al.⁽²³⁾ involving 20 patients with generalized MG, mean age of 64 ± 11 was observed an FVC average of 2.7 ± 0.7 and FEV₁ of 2 ± 0.6. Keenan et al.⁽²⁴⁾ evaluated 17 patients with MG with a mean age of 46 ± 18 years watched an FVC average of 3.4 ± 0.6 and FEV₁ of 2.8 ± 0.5. These values are similar to ours, though observed by Fregonesi et al.⁽²³⁾ are lower, however we consider that the studied patients were older. In both studies also non-obstructive patterns on pulmonary function tests, as well as in our study were observed.

Although breathing is a dynamic event and caused by the variation of inspiratory flow, much can be learned about the inspiratory pump in view of the pressures that can be developed under static conditions. Maximum static pressure generated in the airway opening or through the diaphragm assessments are widely used to characterize the strength of respiratory muscles.^(25, 26)

The amplitude of the variation of pressure checked in the mouth, in a static position for a maximum ventilatory effort is classically used in verifying the ability of the ventilatory muscles, as described by Black and Hyatt for the first time in 1969.⁽²⁷⁾

Black and Hyatt proposed for the first time, the technique in 1969, advocate the use of a mouthpiece circular rigid with a perfect coupling of lips, avoiding air leaks during exhalation. In the course of the test, patients are instructed in how to perform a maximal expiratory pressure.⁽²⁸⁾ Repeated maneuvers maximal inspiratory pressure and maximal expiratory pressure, according Fiz et al.⁽²⁹⁾ does not produce respiratory muscle fatigue when observed between a rest time of the test maneuvers and when there is exaggerated in relation to the number of repetitions. The MIP and MEP are physiologically the most appropriate test to check the ability of the respiratory muscles, and may be recommended as the first option.

The evaluation of the maximum pressure generated by the ventilatory muscles in the mouth is a simple, practical and non-invasive method of verifying muscle function in various pulmonary and neuromuscular pathological conditions.^(28, 30) The findings of Rubinstein⁽³⁰⁾ state that, in adults, ventilatory pressures are higher in men than in women, according to the fact that muscle mass and muscle strength are higher in men compared

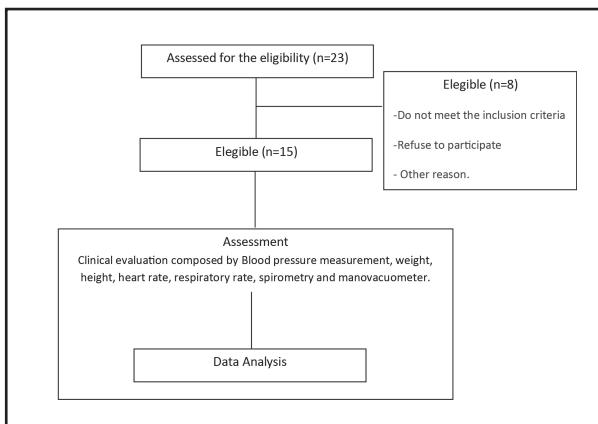


Figure 1. Flowchart of the study.

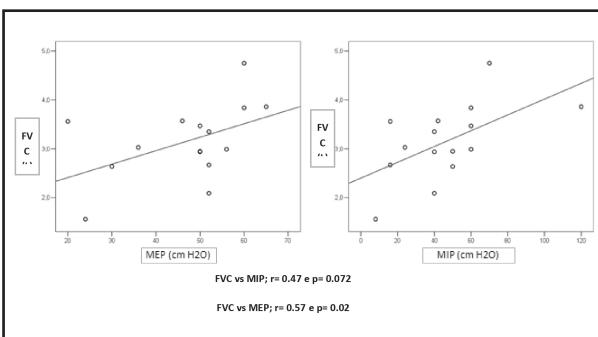


Figure 2. Results of the correlation between the values of forced vital capacity and maximal ventilatory pressures.

to women. These results confirm several other scientific studies conducted previously.

The main factor related to the measurement of the pressure generated by the respiratory muscles is the lung volume. The MIP is higher when starting from residual volume, because the respiratory muscles have a greater mechanical advantage and enjoy the elastic recoil of the chest wall. Conversely, evaluation of MEP is optimized from the condition of total lung capacity, where the expiratory muscles are also in mechanical advantage being assisted by lung elastic recoil.⁽²⁶⁾

The MIP is commonly used to check the pressure generated by the inspiratory muscles ventilation. This is the ability to generate force by the combined muscle contraction during a quasi-static action.⁽³¹⁾ The MIP is indicative of ventilatory capacity and the development of respiratory failure, which is well suited to evaluate the degree of abnormality and monitor the weakening of inspiratory muscles in the evolution of individual patients.⁽³²⁾

A considerable number of terms and abbreviations were used to demonstrate the results of the assessment of maximal inspiratory pressure; including inspiratory force (IF), negative inspiratory force (NIF), negative inspiratory pressure (NIP), maximal inspiratory force (MIF), peak negative pressure (PNP) and maximum static inspiratory pressure (MIP). The maximum static inspiratory pressure is commonly symbolized by MIP or MP. It is important to remember that what really measures is pressure, not force. Therefore, the terminology they use the term strength should be abandoned.

According to Larson,⁽³¹⁾ MIP is set to the highest negative pressure generated in the mouth and held by at least one second. The test shall consist of at least 3-6 effective maneuvers, ie, technically satisfactory, which can not afford air leaks in the nozzle and or action of the buccinator muscles. These are facts that could alter the pressure values assessed. In order to eliminate the action of the muscles of the mouth, there is a hole 1 mm in diameter in the distal portion of the mouthpiece.

It is important to note that evaluations of maximum ventilatory pressures are influenced by gender, age, lung volume and activity of daily living. Another fact to consider is how the number of repetitions of the maneuver. In pulmonary function there is already a consensus on three well-executed maneuvers. However, for the maximum ventilatory pressures have not observed a pattern, getting discretion. Some authors advocate the number of five replicates; others perform more repetitions.⁽³³⁾

Maneuvers to verify the maximal inspiratory pressure should be monitored and be initiated from the respiratory condition of residual volume. This procedure is adopted due to the clinical situation of residual volume to be more reproductive than the functional residual capacity.⁽³¹⁾

Continuing the pulmonary function test, patients breathed for a moment at rest. The MEP was deter-

mined by a sudden forced expiration after a maximal inspiration, reaching the total lung capacity. In each case, efforts have been kept for at least 1 second, and repeated at least 3 times, taking the best performance.

Regarding the maximum pressure generated by the ventilatory muscles, the average value for the MIP of 45.5 cmH₂O among women and the value of 56 cmH₂O for men was observed. To MEP could be observe the average value of 45 cmH₂O for women and 55 cmH₂O for men. The values obtained in our study for maximal ventilatory pressures are under the normal range for healthy people of the same age and sex. In the study by Muñoz-Fernandez⁽³⁴⁾ involving 61 patients with clinically stable MG it was observed the value of 66.9 cmH₂O for MEP and 52 cmH₂O for MIP. Keenan et al.⁽²⁴⁾ in a study involving 17 patients with MG, being thirteen with the generalized form it was observed the values of 67cmH₂O for MIP and 86cmH₂O for MEP. Our values are very coincident with these studies, showing a considerable loss of inspiratory muscle strength in patients with MG.

We would like to draw attention to the spirometry results of our patients who were practically normal, and no evidence of a restrictive or obstructive pattern. The population studied, one patient showed moderate restrictive pattern and other serious, but this patient is 62 years old and has the congenital form. Was also observed in our study a positive correlation between the values of forced vital capacity verified by spirometry and peak values of ventilatory pressures, showing that there is an intimate relationship relationship between pulmonary function and respiratory muscle strength. However, we believe that spirometry is not only a marker of deteriorating clinical condition in these patients because patients with normal pulmonary function showed a significant reduction in respiratory muscle strength.

One of the shortcomings of our study was not conducted to test maximum voluntary ventilation lung function type to investigate the levels of respiratory muscle fatigue. The ventilatory muscle dysfunction can worsen the physical condition of patients with MG, predisposing the onset of myasthenic pattern,^(21,22) reduced lung volumes and contributing to the worsening of symptoms with respiratory manifestations and consequent impairment of quality of life. Therefore, we can say that the evaluation of the maximum pressure generated by the ventilatory muscles is extremely important in the evaluation and follow-up of patients with MG. More studies are needed in order to show the effects of respiratory muscle training programs.

CONCLUSION

At the end of this study we can conclude that patients with MG have lower values of maximal inspiratory pressure and ventilatory espiratórias associated with normal lung function values.

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