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HOW ACCURATE IS SPIROMETRY AT PREDICTING RESTRICTIVE PULMONARY IMPAIRMENT IN CHILDREN WITH MYASTHENIA GRAVIS

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Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction. Clinical symptoms are caused by weakness and increased fatigability of various muscle groups. Myasthenia may lead to significant respiratory dysfunction. The aim of our study was to estimate lung function in children with MG. We tested 23 non-smoking patients (18 girls and 5 boys) aged 7-18 years. Whole-body plethysmography and spirometry were performed in all patients. In 33% of the patients a decrease in VC <80% of predicted value was observed (VC = 89 ±19%), but the analysis of TLC revealed restrictive pattern only in one patient (TLC = 102 ±17%). In more than 75% of the children the value of RV above 120% of predicted value was found (RV = 146 ±54%). Spirometric obstructive pattern measured by FEV_1%VC <70% was not observed, although in 56% of the patients airway resistance was increased (Raw = 132 ±44%). In 45% of the patients a decrease of PEF (76 ±14%) was observed. In MG children true restrictive pulmonary impairment is rarely observed and a decrease in VC in these patents seems to result mainly from functional restriction provoked by an increase in RV. Spirometry is not an optimum method to assess functional changes in MG patients. The assessment of additional measures such as TLC, RV, and Raw is desirable.

Key words: *children, lung function, myasthenia gravis, restrictive pulmonary impairment*

INTRODUCTION

Myasthenia gravis (MG) is a relatively rare autoimmune disorder of peripheral nervous system (1). The annual incidence for MG was reported to range from 1 to 15 persons per 1 million population (2, 3), with the prevalence

from 50-150/10^6 population (4, 5). MG affects people of all ages, and children constitute only approximately 10-15% of them (6). MG is a potentially serious but treatable muscle disease caused by autoantibodies directed at the acetylcholine receptor (AChR) on the postsynaptic membrane of the neuromuscular junction (7). Acetylocholine receptor antibodies are present in about 50% of patients with ocular and in 90% with generalized MG (1). Muscle weakness and fatigue are caused by abnormalities in neuromuscular transmission. The disease varies from mild cases with purely ocular symptoms to severe cases with generalized weakness and respiratory insufficiency. Weakness and fatigability of bulbar and respiratory muscles may cause myasthenic crises with respiratory insufficiency (8). Therefore monitoring of respiratory function is important in MG patients.

Neuromuscular diseases lead to the weakness of respiratory muscles with restrictive ventilatory impairment (8). For many years a decrease of vital capacity (VC) measured by spirometry has been the main criterion of restrictive pattern. Currently a decrease of VC is no longer sufficient for the diagnosis of a restrictive pulmonary defect and the measurement of total lung capacity (TLC) by whole-body plethysmography is necessary (9).

The aim of our study was to estimate lung function in children with MG and appreciate the accuracy of spirometry at predicting restrictive pulmonary impairment in children with MG.

MATERIAL AND METHODS

We evaluated 23 never-smoking patients (18 girls and 5 boys) aged 7-18 (13.4 ±3.4) years. The diagnosis of MG was based on clinical symptoms and the evidence of neuromuscular transmission defect documented with repetitive nerve stimulation test (RNS) or single fiber electromyography (SFEMG). RNS of the radial, accessory or femoral nerve was performed in all cases. If the result was normal, SFEMG was done with the voluntary activation of the extensor digitorum communis or frontalis muscle (9). The clinical status of the patient was graded with Myasthenia Gravis Foundation Association (MGFA) scale (10). The patient was considered seropositive if acetylcholine antibodies were >0.4 nmol/l. RNS confirmed the diagnosis in 17 patients, SFEMG was abnormal in the remaining 6. There were 19 (83%) of sero-positive patients. The mean antibody level was 11.8 (0.5-56.6) nmol/l. Four patients had ocular myasthenia (class I MGFA). Generalized myasthenia was classified as IIa in 3, IIb in 8, IIIb in 5, IVa in 2, and IVb in one patients. All patients were symptomatic and treated with pirydostygmine bromide (Mestinon). Lung function tests were usually performed 4 h after one tablet (60 mg) of Mestinone. Eight patients were treated with thymectomy, at least 6 mo before lung function tests were performed.

Measurements of vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and FEV_1%VC in spirometry were expressed as a percentage of the predicted values to control for the influence of age, gender, and height. According to the American Thoracic Society standards, a minimum of 3 acceptable and reproducible maneuvers were obtained (11). Reference values according to ERS guidelines were applied (12). The possibility of restrictive pulmonary impairment was defined as VC lower than 80% of predicted. Flow-volume loops

enabled to measure the peak expiratory flow (PEF) and maximal expiratory flows (MEF75, MEF50 and MEF25).

The fundamental function of whole-body plethysmography is to measure residual volume (RV), total lung capacity (TLC), functional residual capacity (FRC), and airway resistance (Raw). A decrease of PEF<80% and MEF50<60% (without obstructive or restrictive pattern) was considered as abnormal. In all cases spirometry and whole body plethysmography were performed according to ERS standards (12, 13) by experienced staff using a Sensor Medics equipment (USA). Restrictive ventilatory defect was defined as TLC lower than 80% of predicted and an obstructive ventilatory impairment as $FEV_1/VC<0.7$ (11). An increase of RV>120% and Raw>120% of predicted was considered as abnormal.

The data are presented as mean ±SD. Pearson's test was used for statistical analysis and $P<0.05$ was regarded as indicative of statistically significant differences (Statistica 6 for Windows).

RESULTS

None of the tested patients had obstructive pattern in spirometry. The mean FEV_1%VC was 90 ±7% and the mean FEV_1 was 89 ±20 (*Fig. 1*). In 7 patients, FEV_1 was below 80% of predicted, which was always provoked by a decrease in VC. The mean VC was in a normal range of 89 ±18.8%, but in 33% of the patients tested a VC<80% was found (suspected restrictive pattern) (*Fig. 1*). However, only in 1 patient the analysis of TLC revealed restrictive ventilatory impairment and 7 patients with decreased VC represented functional restrictive impairment provoked by an increase in RV (*Fig. 2*). The mean TLC was 102 ±17% of predicted (*Fig.1*). In the majority of the MG patients tested (72%) an increase in RV was found (*Fig. 3*). The mean RV increased to 146 ±54% of predicted (*Fig 1*). An increase of FRC was considerably less frequent as it was observed only in 32% of the patients (mean FRC = 111 ±25%) (*Fig. 3*).

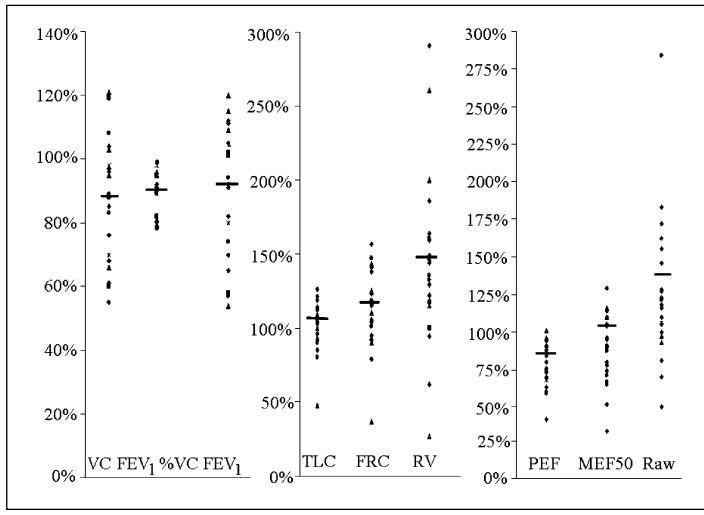

Fig. 1. Distribution of spirometric and plethysmographic results myasthenia gravis patients.

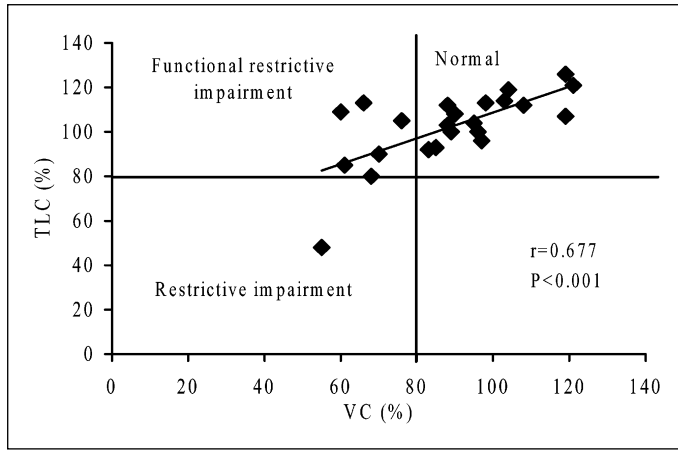

Fig. 2. Accuracy of spirometry at predicting restrictive pulmonary impairment in children with myasthenia gravis

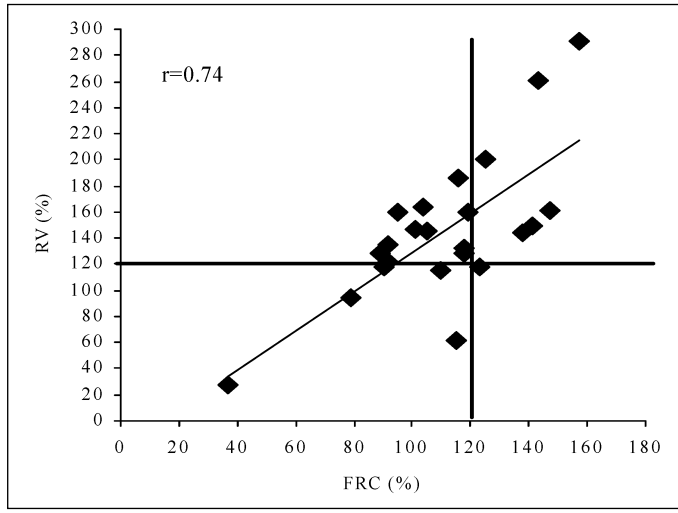

Fig. 3. Correlation between FRC and RV.

In 56% of the patients airway resistance (Raw) increased (Raw = 128 ±44%). In 45% of the patients a decrease in PEF (76 ±14%) was observed (*Fig. 1*). The mean value of MEF50 in MG patients remained in a normal range (MEF50 = 89 ±22%). A negative correlation was found between Raw and both RV and FRC (*Fig. 4*). Negative correlation was also observed between VC and RV/TLC, but not directly between VC and RV (*Fig. 5*).

A small number of patients in the MGFA groups did not allow for statistical comparison between them. However, pseudorestrictive changes were detected only in the patients with generalized MG. The only patient with reduced VC and TLC was in the group IVb of MGFA.

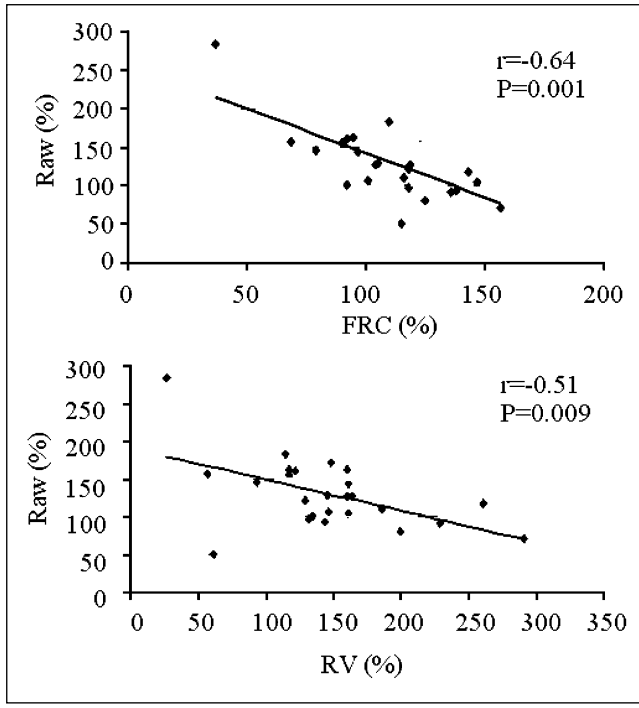

Fig. 4. Correlations between Raw and both FRC and RV.

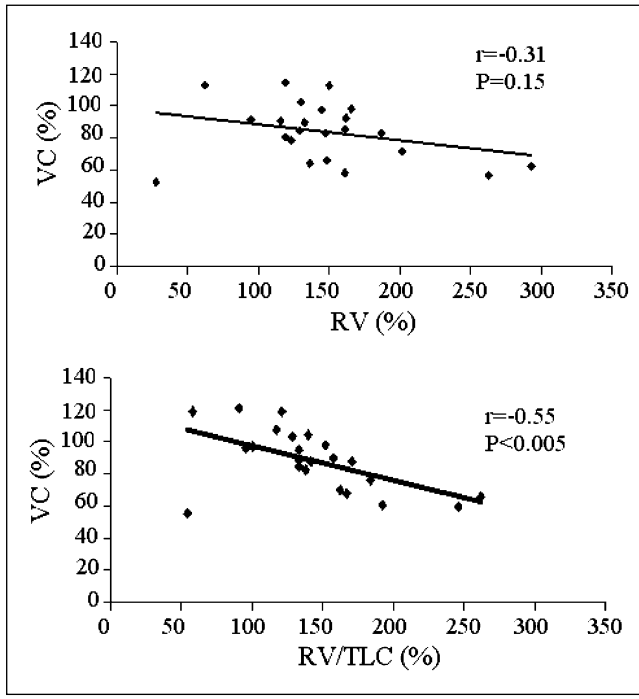

Fig. 5. Correlations between VC and both RV and RV/TLC.

DISCUSSION

Previous studies of lung function tests of non-treated MG patients demonstrated reduction of VC, interpreted as restrictive ventilatory defect due to weakness of respiratory muscles (15, 16). The aim of the present study was to verify suspected restrictive defects in spirometry by assessing also TLC in the whole-body plethysmography. Although in our study VC correlated with TLC (r=0.68), only 1 of the 7 patients with VC<80% fulfilled the criteria of restriction (TLC<80%) (*Fig. 2*). He had a severe generalized and bulbar muscle weakness (group IVb MGFA). Despite that respiratory changes in MG are considered purely restrictive, our patients showed VC reduction due to increased RV, compatible with pseudorestriction.

The presence of pseudorestriction in the majority of MG cases makes spirometry an insufficiently sensitive method to detect restrictive pulmonary impairment in such patients. Therefore, our failure to observe the obstructive pattern in the MG patients, as measured by FEV_1%VC<70%, could be a spurious finding. Pseudorestrictive defects (i.e., a VC reduction with normal or even increased TLC) often occur with obstructive diseases, with increased FRC (17). Although MG could be defined as a pure restrictive disease, our patients showed a VC reduction in spirometry due to increased RV.

In an earlier study on juvenile MG, no other than a reduced PEF functional respiratory impairment was observed (17). That work, however, presents only the mean results. If the mean VC value amounts to 86 ±21%, it is likely that some of the patients examined had VC below 80%, suggesting restriction (18). Unfortunately, the authors failed to report individual results or the percentage of patients with significant VC reduction. The TLC results are not given either (18). The disease can show various degrees of advancement and involves various muscular groups. Hence, average results do not provide the whole picture of the problem, since they fail to divide patients into groups with and without functional impairment. To assess RV the authors selected the thoracic gas volume (TGV). It corresponds to the FRC, i.e., the sum of RV and ERV (expiratory reserve volume). This parameter reflects resting lung function at the end of calm expiration, but it fails to reflect univocally the RV. The mean value of TGV of 108 ±20% was similar to the value of FRC (111%) obtained in our study. Indirectly, it may be assumed that with the observed standard deviation, certain patients had increased RV. It is interesting to see that although RV>120% was observed in the majority of patients (72%), increased FRC was recorded only in 32%. Hence, increased RV is a consequence of a reduction, often significant, of ERV, thereby not reflecting an increased FRC level of calm expiration in the majority of patients. Increases in RV and FRC often occur in obstructive diseases as an expression of peripheral distention secondary to bronchoconstriction. In the present study, MG patients did not show obstruction measured by FEF1%VC<70%, but some patients had increased Raw. However, a negative

correlation of RV and FRC with resistance was observed. This proves that an increase in RV was not provoked by bronchoconstriction, but, rather, by weakness of bulbar or respiratory muscles.

On the other hand, Spinelli et al (18) observed in MG patients a reduction of VC with an accompanying increase of RV and RV/TLC similar to our results. Spirometry is not sufficient to assess functional impairment of respiratory system in MG patients; it is worthwhile to expand examination by adding plethysmography. Out of all variables measured by spirometry, the PEF is the most useful, often reduced in some MG patients (18, 20). The PEF value depends upon the strength of expiratory muscles (21).

Treatment has an important influence on respiratory function in MG patients. Radwan et al (21, 22) described a partial improvement of lung function following the application of pirydostygmine bromide and after thymectomy. The authors observed a reduction in VC in their patients. They failed, however, to analyze individual TLC values. Nevertheless, the increased mean RV of 153 ±44% in 16 patients aged 24-49 years compared with that of the normal reference group of 96 ±12% was underscored (22). The measurement of muscle weakness showed that it was more pronounced in inspiratory than expiratory muscles (22). Indirectly, it points to the possibility of reduced PEF observed in our patients. A direct comparison of results of lung function tests reported by different authors is not possible due to different severity of MG symptoms. Although our limited data did not allow comparing plethysmographic parameters between the MGFA groups, there was a tendency toward an increase in RV and, less pronounced, toward a decrease in VC in generalized MG.

We conclude that true restrictive pulmonary impairment in young patients with MG is rarely observed and a decrease in VC is a consequence of functional restriction by an increase in RV. A decrease of PEF and an increase of Raw are important functional respiratory changes in young patients with MG. Spirometry may not sufficiently assess functional changes in MG patients. It is, therefore, worthwhile to assess TLC, RV, and Raw as well.

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