

Expiratory muscle strength as a predictor of functional exercise capacity in generalized myasthenia gravis

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ABSTRACT

الأهداف: دراسة العلاقات بين اختبار المشي لمدة 6 دقائق وشدة المرض والوظائف الرئوية وأداء العضلات التنفسية لدى المرضى الذين يعانون من الوهن العضلي العام (MG) ولتحديد ما إذا كانت شدة مرض MG ووظائف الرئة وأداء العضلات التنفسية تسهم في المسافة لاختبار المشي لمدة 6 دقائق سيراً في MG.

الطريقة: أجريت هذه الدراسة المستعرضة في جامعة هاسيتيب في أنقرة، تركيا. أجريت الدراسة خلال الفترة من فبراير إلى أغسطس 2017م. شارك 28 من مرضى MG من II إلى III في الدراسة. تم تحديد شدة مرض المرضى مع مقياس الوهن العضلي المركب. خضع جميع المشاركين لاختبار المشي لمدة 6 دقائق، واختبارات وظائف الرئة، وقوة العضلات التنفسية وتقييم القدرة على التحمل.

النتائج: كان حوالي 40% من قوة عضلات الزفير لدى المرضى تحت الحد الأدنى الطبيعي. كشف تحليل الانحدار الخطي المتعدد أن النسبة المئوية لقوة عضلات الزفير المتوقعة التي توصل إليها المرضى كانت مؤشراً هاماً ومستقلاً للنسبة المئوية لمسافة اختبار المشي لمدة 6 دقائق التي توصل إليها المرضى وفقاً للقيم المرجعية. ($R^2=0.493$, $F [1-27]=25.275$, $p<0.001$).

الخلاصة: قوة عضلات الزفير هي أحد المحددات الهامة لأداء التمارين الوظيفية في MG العام مع وجود ضعف خفيف أو معتدل يؤثر على العضلات الأخرى غير عضلات العين.

Objectives: To investigate the correlations between the 6-minute walk test and disease severity, pulmonary functions, and respiratory muscle performance in patients with generalized myasthenia gravis (MG) and to determine whether MG disease severity, pulmonary functions, and respiratory muscle performance contribute to 6-minute walk test distance in generalized MG.

Methods: This cross-sectional trial was conducted at Hacettepe University in Ankara, Turkey. The study was carried out from February to August 2017. Twenty-eight class II-III MG patients participated in

the study. Patients' disease severity was determined with the Myasthenia gravis composite scale. All participants underwent the 6-minute walk test, pulmonary function tests, and respiratory muscle strength and endurance assessment.

Results: Approximately 40% of patients' expiratory muscle strength were under the lower limit of normal. Multiple linear regression analysis revealed that the percentage of predicted expiratory muscle strength that patients reached were significant and independent predictor of percentage of 6-minute walk test distance that patients reached according to reference values ($R^2=0.493$, $F [1-27]=25.275$, $p<0.001$).

Conclusion: Expiratory muscle strength is a significant determinant of functional exercise performance in generalized MG with mild or moderate weakness affecting muscles other than the ocular muscles.

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Myasthenia gravis (MG) is an autoimmune disease caused by antibodies against components of the postsynaptic membrane at the neuromuscular junction. These antibodies block function by binding to their target and inducing antigen crosslinking, complement activation, and increased degradation. These cause muscle fatigue and weakness in patients with MG.¹ Comorbid conditions may be critical for quality of life,

daily functions, short- and long-term outcome, and mortality in MG patients.²

Inspiratory and expiratory muscle strength is shown to be reduced in patients with generalized MG compared to controls or ocular MG patients.³⁻⁵ Patients with MG often have a “myasthenic pattern” characterized by reduced ventilatory muscle endurance and volumes in lung function tests.^{6,7} Patients usually report dyspnea upon extreme effort due to muscle weakness, and ventilatory muscle impairment adversely affects the performance of physical activities and patients’ daily lives due to perceived fatigue.⁸

The 6-minute walk test (6MWT) has been shown to be relatively reliable in patients with neuromuscular diseases and 6MWT distance (6MWD) was reported to be lower in generalized MG patients than in healthy controls.^{8,9} In addition, composite disease severity scales have become increasingly important to show prognosis. The myasthenia gravis composite scale (MGCS) is a reliable, valid, and easily applicable instrument for assessing the clinical status of MG patients and differs from other MG severity scales because it incorporates physician-reported and patient-reported test items.¹⁰

Therefore, the aims of this study were: to investigate correlations between 6MWD and pulmonary functions, respiratory muscle performance, and MG severity determined by the MGCS in patients with generalized MG and to determine whether disease severity assessed by a composite score, pulmonary functions, and respiratory muscle performance contribute to or reflect decreased functional exercise capacity in generalized MG.

Methods. Subjects. This cross-sectional study was carried out in Hacettepe University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation Ankara, Turkey between February-August 2017. Myasthenia gravis was diagnosed with single fiber electromyography testing or demonstration of anti-acetylcholine receptor antibodies. Inclusion criteria were: age 18-65 years; diagnosis of MG made by a neurologist; and generalized symptoms (Myasthenia Gravis Foundation of America [MGFA] clinical class II-III). Exclusion criteria were presence of; comorbid neuromuscular and cardiopulmonary pathologies; severe limb, axial, oropharyngeal, or respiratory muscle weakness (MGFA class IV); and MG crisis (MGFA class V). The study was approved by the Hacettepe

University Non-Interventional Clinical Research Ethics Board (approval number: GO 16/814-24). All patients signed an informed consent form before participating. A single group pre-test and post-test design were used.

Assessments. The patients’ physical characteristics (height, weight, gender), sociodemographic data, and disease course (disease duration and medication history) were recorded. Perceived general fatigue severity was assessed using the visual analog scale (VAS).

The patients’ clinical status was determined with the MGCS. The MGC scale consists of 10 items that measure signs and symptoms of MG with weighted response options. The MGCS is easy to administer, takes less than 5 minutes to complete, and requires no equipment. The test items selected are meaningful to both the physician and the patient and responsive to clinical changes. The MGCS scale can be used in everyday practice and in clinical trials.¹⁰

Pulmonary function tests (PFT) were performed with a Fitmate MED Spirometer (Cosmed, Rome, Italy) according to American Thoracic Society and European Respiratory Society criteria PFT results were expressed as percentages of predicted values and were adjusted for age, height, body weight, and gender.¹¹

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured with a portable electronic mouth pressure device (Micro Medical Micro MPM, UK).

Maximal inspiratory pressure was measured at residual volume and MEP was measured at total lung capacity (TLC).¹² Values were expressed as percentages of predicted values according to age and gender and lower limit of normal for MIP and MEP values were calculated.¹³

To evaluate respiratory muscle endurance, constant load testing at threshold load was applied. The time that could be sustained at an inspiratory load of 60% MIP was recorded. The patients were asked to breathe at a fixed inspiratory load equal to 60% MIP on a pressure threshold loading device (Powerbreathe, POWERbreathe International Ltd., Warwickshire, England). Failure to continue breathing against this resistance at any time point earlier than 10 minutes was considered impaired respiratory muscle endurance.¹⁴ In our previous study, this test was found to be reproducible and show minimal learning effect.¹⁵ In addition, constant load endurance tests reflect respiratory muscle endurance capacity better than incremental loading endurance tests.¹⁴

The 6MWT plays a key role in evaluating functional exercise capacity, assessing prognosis, and evaluating response to treatment across a wide range of diseases.

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The 6MWT is a self-paced test of walking capacity. Patients were asked to walk as fast as possible along a flat 30-meter corridor for 6 minutes. The 6MWD was recorded in meters. Standardized instructions and encouragement were given during the test. In pre- and post-test periods, heart rate (HR) and oxygen saturation (SpO₂) values were recorded by pulse oximeter (Veron, Shenzhen Aeon Technology Co. Ltd). General fatigue perception in pre- and post-test periods was assessed with the modified borg scale (MBS). The MBS is a 0-10 rated scale that can be used to measure dyspnea, fatigue perception, or rate of perceived exertion. Higher scores indicate greater symptom severity. The 6MWT was conducted approximately 1-2 hours after taking pyridostigmine. Patients performed the test twice, 30 minutes apart, on the same day and the longer distance was used for statistical analysis.¹⁶ Percentage of predicted 6MWD according to age and gender (%6MWD) and 6-min walk work (6MWW; 6MWD x body weight) were calculated.^{16,17}

Statistical analysis. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 18.0 software for Windows (SPSS Inc., Chicago, IL, USA). Variables were expressed as mean±standard deviation, frequency, percentage, median, minimum, and maximum. Normality was evaluated with the Shapiro-Wilk test. Correlations were analyzed using Pearson correlation analysis because the data met parametric assumptions.¹⁸ Correlations were classed as strong ($r>0.70$), moderate ($r=0.50-0.69$), weak ($r=0.26-0.49$), and very weak/no correlation ($r=0.00-0.25$).¹⁹ The parameters affecting %6MWD were investigated using Spearman/Pearson correlation. A multiple linear regression analysis with backward elimination was carried out to identify independent predictors of %6MWD.²⁰ A post hoc power analysis was performed using the G*Power statistical program (G*Power 3.0.10 software).²¹ Statistical tests were two-tailed and a p -value<0.05 was considered statistically significant.¹⁸

Results. Of 50 MG patients who were referred to our unit, 22 did not meet the eligibility criteria. Therefore, the study included 28 patients (15 females) with clinically stable MG. Anthropometric and demographic characteristics are described in Table 1. According to MGFA classification, 14.3% of the patients were class IIa, 42.9% were class IIb, 14.3% were class IIIa, and 28.6% were class IIIb. All patients were receiving the anticholinesterase drug pyridostigmine at varying doses (240-360 mg/day) based on disease severity. Eighteen patients have chronic prednisone use.

The patients' spirometric values, maximum respiratory pressures (MIP and MEP), respiratory muscle endurance time, and 6MWT results are presented in Table 2. Patients showed restrictive pattern and mild reduction in vital capacity. Patients had approximately 93% of predicted inspiratory muscle strength and approximately 85% of predicted expiratory muscle strength according to their age and gender. All patients' MIP values were within normal range, while 39.3% of MEP values were below the lower limit of normal. Mean respiratory muscle endurance time was 42.5 seconds (<10 min). Mean 6MWD was 459.32 and %6MWD was nearly 81%. Patients reached approximately 68% of maximal HR during the 6MWT.

Correlations between clinical status, pulmonary functions, respiratory muscle strength, and functional capacity in patients with MG are presented in Table 3. Percentage of predicted 6MWD was inversely related with MGCS score ($r=-0.600$, $p=0.001$) and positively correlated with MEP ($r=0.510$, $p=0.006$), %MIP ($r=0.403$, $p=0.034$) and %MEP ($r=0.689$, $p<0.001$). Multiple linear regression analysis revealed that %MEP was a significant and independent predictor of %6MWD ($R^2=0.493$, $F(1-27)=25.275$, $p<0.001$), (Table 4). Post hoc power analysis was carried out on our 6MWT data using the results of Gibbons et al,²² ($d=2.237$, $\alpha=0.05$ [two-tailed]). Power ($1-\beta$) was higher than 99%.

Discussion. The main findings of our study were the presence of reduced respiratory muscle endurance and the onset of expiratory muscle weakness in patients with class II-III generalized MG. Myasthenia gravis disease severity determined by MGCS was moderately correlated with general fatigue severity, pulmonary functions, and functional exercise capacity. Functional

Table 1 - Baseline patients with MG characteristics (n=28).

Variables	Median (min-max) OR (95% CI)
Age (years)	53.5 (24-65)
Gender (male/female)	13/15
Height (cm)	165.5 (153-181)
Weight (kg)	70 (40-103)
BMI (kg/m ²)	25.00 (16.07-36.26)
Disease duration (years)	4 (1-18)
The MGCS score	10 (0-26)
Fatigue severity (VAS)	5 (0-10)

MG - Myasthenia gravis, OR - odds ratio, CI - confidence interval, BMI - body mass index, MGCS - myasthenia gravis composite scale, VAS - visual analog scale

Table 2 - Pulmonary functions, strength and endurance of respiratory muscles and parameters of 6 minute walk test in patients with MG (n=28).

Variables	Mean±SD
FEV ₁ (%)	74.72±17.93
FVC (%)	71.60±16.71
FEV ₁ /FVC	85.32±7.72
VC (%)	75.54±15.36
MIP (cmH ₂ O)	81.86±22.85
%MIP	92.90±22.29
MEP (cmH ₂ O)	90.21±37.49
%MEP	85.36±35.59
6MWD (m)	459.32±87.58
%6MWD	80.08±16.93
6MWW	32599.34±8112.72
%Maximal HR	67.23±12.85
ΔHR (beats/min)	27.29±18.38
ΔSpO ₂ (%)	-0.64±1.59
ΔGeneral fatigue (modified borg)	3 (0-10)
Respiratory muscle endurance time (sec) Median (min-max)	42.5 (11-180)

SD - standard deviation, MG - Myasthenia gravis, FEV₁ - forced expiratory volume in one second, FVC - forced vital capacity, VC - vital capacity, MIP - maximal inspiratory pressure, MEP - maximal expiratory pressure, 6MWD - 6 minute walk test distance, 6MWW - six minute walk work, HR - heart rate, SpO₂ - oxygen saturation.

exercise capacity measured using the 6MWT was moderately associated with inspiratory and expiratory muscle strength. We also showed that expiratory muscle strength was a significant determinant of functional exercise performance, accounting for approximately 50% of the variance in %6MWD.

Many patients with MG have a restrictive pattern on PFT.^{3,5,23,24} Mean vital capacity (VC) in the present study (75.54±15.36%) was similar to that reported by Mier-Jedrezejowicz et al,²³ in generalized mild-to-moderate MG (70.9±19.0% of predicted). Patients in our study showed minimal restrictive pattern because only MGFA class IIa-IIIb patients were included. Keenan et al,³ reported lower MIP and MEP values and lower respiratory muscle endurance in generalized MG patients than control or ocular MG groups. Mean %MIP was 70% and %MEP was 50%. The slightly higher mean values observed in our study (%MIP was 92.90% and %MEP was 85.36%) may be related to our inclusion of patients with mild/moderate weakness only, and exclusion of those with ocular MG, acute respiratory crisis, and poor drug response. Early in the course of MG, only 1-4% of patients exhibit respiratory muscle impairment; however, this rate reaches 60-80%

in later stages.²⁵ Patients with generalized MG have significant generalized, fixed muscle fatigable weakness mostly affecting the shoulder abductors, hip flexors, and neck muscles, and loss of muscle strength does not seem to be associated with disease duration.^{26,27} More than a quarter of patients in our study had expiratory muscle weakness, which shows that abdominal muscles may be more affected as a peripheral muscle in generalized MG.^{26,27} Our findings are consistent with those of Ringqvist et al,²⁴ who reported a smaller decrease in MIP than MEP in moderate MG, and respiratory muscle endurance was very low in accordance with the literature.³

The distance walked in the 6MWT reveals limitations in functional capacity and there is a moderate to strong relationship (range: 0.4-0.8) between 6MWD and peak oxygen consumption (VO₂) in incremental cardiopulmonary exercise testing.²⁷⁻²⁹ The mean 6MWD of MG patients was 459.32±87.58 and this value is comparable to normal values in healthy subjects.²² Our patients also reached 80% of predicted values and this is acceptable as close to normal (>82% of predicted reference values).²⁹ We also showed that 6MWT distance is moderately associated with inspiratory muscle strength and disease severity. Because our patients had normal inspiratory muscle strength and moderate disease severity, this is an expected finding. In addition, our patients reported a modest increase in general fatigue during the test. Although their preserved functional exercise capacity, chronic prednisone use of 65% of patients could have limited their walking capacity.

The prevalence of fatigue in MG is estimated as 75% to 89%.^{29,30} Elsaï et al,³⁰ showed that the MG questionnaire, an indicator of clinical status, is associated with fatigue scores and functional level in patients with non-severe MG (MGFA 0-II). Our study also demonstrated that disease severity assessed by MGCS was moderately correlated with fatigue severity, pulmonary functions, and functional exercise capacity. This finding could increase the clinical usefulness of the MGCS score.

The multiple linear regression analysis in this study showed that approximately half of the variance in %6MWD was explained by %MEP in generalized MG with mild/moderate weakness. This finding reveals that lower expiratory muscle strength result in lower functional exercise capacity in MG patients. In addition, in accordance with the literature on other health conditions,^{31,32} we identified a moderate relationship between inspiratory muscle strength and walking

Table 3 - The correlations between clinical status, pulmonary functions, respiratory muscle strength and functional capacity in patients with MG (n=28).

Variables	Fatigue severity (VAS)	FEV ₁ (%)	FVC (%)	FEV ₁ /FVC (%)	VC (%)	6MWD	%6MWD	6MWW
The MGCS score	r=0.520*	r=-0.552*	r=-0.558*		r=-0.546*	r=-0.600*	r=-0.464*	r=-0.466*
FVC (%)						r=0.415*		
MIP						r=0.586*		r=0.377*
MEP							r=0.510*	r=0.405*
%MIP						r=0.588*	r=0.403*	
%MEP							r=0.689*	

MG - Myasthenia gravis, MGCS - myasthenia gravis composite scale, VAS - visual analog scale, FEV₁ - forced expiratory volume in one second, FVC - forced vital capacity, VC - vital capacity, MIP - maximal inspiratory pressure, MEP - maximal expiratory pressure, 6MWD - 6 minute walk test distance, 6MWW - six minute walk work, HR - heart rate, *p<0.05 Spearman correlation test.

Table 4 - Multiple linear regression analysis (n=28).

Variables in the model	R	R ²	Adjusted R ²	SE of the estimate	B	SE	P-value
%MIP, MEP, %MEP, The MGCS score	0.754	0.568	0.493	12.056	56.186	14.167	0.001
MEP, %MEP, The MGCS score	0.748	0.560	0.505	11.917	63.408	9.080	<0.001
%MEP, The MGCS score	0.731	0.535	0.498	11.999	61.704	9.022	<0.001
%MEP	0.702	0.493	0.473	12.285	51.566	6.128	<0.001

Dependent variable: %6MWD, Independent variables: MEP, %MEP, %MIP, the MGCS, MGCS - myasthenia gravis composite scale, MIP - maximal inspiratory pressure, MEP - Maximal expiratory pressure, SE - standard error, R²=0.493, F_(1,27)=25.275, p<0.001, constant=51.566.

capacity in MG. Considering that peripheral muscle strength is a strong determinant of 6MWD in chronic lung disease and our patients did not exhibit marked inspiratory muscle weakness, expiratory (trunk skeletal) muscle strength may be a predictor of %6MWD in patients with class II-III MG.^{31,33}

Limitations. The main limitation of this study is not including class I or IV-V patients. This prevents the generalization of our results to all MG patients. Because it is a rare disease and the study only included class II-III MG, the included patient number is rather small, and the lack of a control group in the study is another limitation. The evaluation of general fatigue perception with VAS may also be relatively subjective. In addition, the last pyridostigmine dose (1-2 hour before the test) and variable time of day could have affected 6MWT performance. In addition, 65% of patients were using prednisone. Future studies may be designed to assess exercise capacity with and without this type of drugs.

In conclusion, our findings demonstrate that the evaluation of MEP may be important in clinical practice because it can provide information about patients' functional exercise capacity. Myasthenia gravis disease severity and inspiratory muscle strength are associated with 6MWT performance. Although MG patients show a marked decrease in respiratory muscle endurance, it does not seem to contribute to functional impairment. In addition, greater MG severity is associated with more severe general fatigue, reduced pulmonary functions, and lower functional exercise capacity in generalized MG.

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