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Ventilatory muscle strength and endurance in myasthenia gravis

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Ventilatory muscle strength and endurance in myasthenia gravis. S.P. Keenan, D. Alexander, J.D. Road, C.F. Ryan, J. Oger, P.G. Wilcox. ©ERS Journals Ltd 1995.

ABSTRACT: Patients with generalized myasthenia gravis (MG) often have associated ventilatory muscle involvement. It is not known whether patients with isolated ocular muscle involvement have identifiable involvement of their ventilatory muscles. Most studies have assessed muscle involvement by measuring muscle strength; however, we hypothesized that measures of ventilatory muscle endurance may be more sensitive tests of ventilatory muscle involvement in myasthenia gravis.

We studied 17 patients with myasthenia gravis (four with ocular involvement alone and 13 with varying degrees of generalized myasthenia gravis). Spirometry, ventilatory muscle strength (maximum inspiratory and expiratory pressures (MIP and MEP)) and endurance (2 min incremental threshold loading test) were measured before and 20 min after i.m. neostigmine. We compared the results with those of 10 normal controls.

We found no difference between patients with isolated ocular involvement and controls. Ocular myasthenia gravis patients did not improve after neostigmine. The patients with generalized myasthenia gravis had reduced baseline ventilatory muscle strength (MIP 67 cmH_2O (70% of predicted), MEP 86 cmH_2O (50% of pred) and endurance (mean maximal load achieved = 246 g, mean pressure at highest load ($\bar{P}$) = 19.4 cmH_2O) compared with controls. After neostigmine, there was a significant increase in MIP in patients with generalized myasthenia gravis and a trend towards an increased MEP. As a group, the patients with generalized myasthenia gravis did not demonstrate a change in their ventilatory muscle endurance after neostigmine; however, there was considerable interpatient variability in response.

We conclude that patients with isolated ocular MG have normal ventilatory muscle strength when tested conventionally. The measurement of ventilatory muscle endurance by incremental threshold loading does not provide additional information to the measurement of ventilatory muscle strength in patients with generalized myasthenia gravis.

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Myasthenia gravis is a disorder of neuromuscular transmission that results from an antibody-mediated blockade of muscle nicotinic acetylcholine receptors. This disorder is characterized by weakness of voluntary muscles, accentuated by repetitive activity, and alleviated by rest and cholinesterase inhibitors. Ventilatory muscle weakness has been demonstrated in patients with generalized myasthenia gravis [1, 3–6], and increased strength reported following the administration of cholinesterase inhibitors [2–7]. Whether clinically significant ventilatory muscle weakness exists in patients with milder or predominantly ocular muscle weakness has not been established.

Most studies to date have assessed ventilatory muscle involvement in myasthenia gravis by measuring muscle strength using maximal static respiratory pressures [2, 4–6]. Given the pathogenesis of myasthenia gravis, an assessment of ventilatory muscle endurance may be a more sensitive indicator. Ventilatory muscle endurance has previously been assessed using maximum voluntary ventilation [6] and 15 s sustained maximal inspiratory effort [4]. Both of these tests, however, have important limitations in the assessment of endurance. During maximum voluntary ventilation, the measured variable is highly dependent on flow rates, and thus maximal performance can be limited by pulmonary parenchymal rather than muscle factors [8]. Maximal sustained inspiratory effort may reflect muscle strength rather than muscle endurance. Because of the propensity to increased fatigability in myasthenia gravis, tests that incorporate repetitive muscle contractions may be more sensitive in detecting ventilatory muscle involvement than tests of muscle strength. The 2 min incremental threshold loading test is such a test of ventilatory muscle endurance [8–12].

Our objectives in this study were: 1) to evaluate symptoms of dyspnoea and measurements of spirometry, respiratory muscle strength and endurance in patients with a spectrum of severity of myasthenia gravis; and 2) to determine whether incremental threshold loading, a measurement of ventilatory endurance, was more sensitive than maximal static respiratory pressures in detecting ventilatory muscle involvement or response to cholinesterase inhibitors.

Methods

Patients

Seventeen patients (9 males and 8 females) with myasthenia gravis were recruited from the neurology service at the University of British Columbia Hospital, Vancouver, Canada. Four patients had isolated ocular muscle involvement and 13 had generalized myasthenia gravis (muscles other than ocular clinically involved). Diagnosis and categorization were based on a detailed neurological examination (J.O.), electromyographic (EMG) studies, and testing for the presence of acetylcholine receptor antibodies. The patients' duration of their disease ranged from 2 months to 39 yrs (mean 9.4 yrs) (table 1). Their height ranged 160–189 cm (mean 171 cm) and their weight 53–110 kg (mean 75 kg). Fifteen were positive on testing for serum antibodies against human acetylcholine receptor (three patients with ocular and 12 with generalized myasthenia gravis). Two were negative for serum antibodies (one of whom had ocular myasthenia gravis). These two patients were diagnosed by a combination of compatible clinical examination findings, EMG studies and appropriate response to therapy. Four patients had undergone a thymectomy. Eight patients were receiving prednisone (with doses varying from 15 mg every other day to daily dosing of 50 mg), two azathioprine (one in combination with prednisone), and one cyclosporin (in combination with prednisone). The patients' functional status was classified according to the OSSERMAN [13] grade (table 1). None of the patients had a prior history of respiratory disease.

Ten volunteers (five females) who had no prior history of respiratory or cardiac disease served as controls. Age, height and weight did not differ between controls and myasthenia gravis patients; ocular or generalized (table 1).

Techniques

Dyspnoea was assessed using the Baseline Dyspnoea Index as described by MAHLER *et al.* [14]. In this index, a patient's functional impairment, magnitude of task and effort causing shortness of breath are scored from 0 (most impaired) to 4. A maximum score of 12 is possible.

All patients and controls had spirometry measured using the Breon spirometer model 2400 (Breon Laboratories Inc., New York, NY, USA); forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were expressed as percentage predicted (from MORRIS *et al.* [15]) as well as in absolute values.

Respiratory muscle strength and endurance were measured in each group. The maximum inspiratory pressure (MIP) was measured after a maximal inspiratory effort from near residual volume (RV), and maximum expiratory pressure (MEP) after maximal expiratory effort from near total lung capacity (TLC). The maximum pressure was taken as the highest of five attempts sustained for a minimum of one second and expressed as percentage predicted using the values of BLACK and HYATT [16].

Respiratory muscle endurance was measured using a 2 min incremental threshold loading test [7]. Figure 1 illustrates the weighted plunger and inspiratory port with an orifice of 6.6 mm^2. Adding weights to the plunger increased the pressure required to open the inspiratory port when the stopper was in place. Inspiratory pressures were measured at the mouth with a differential ±350 cmH_2O pressure transducer (model DP45-16, Validyne Co, Northridge, CA, USA). Peak inspiratory mouth pressure with each breath and mean mouth pressure ($\bar{P}$) were recorded. The $\bar{P}$ was obtained on line by passing the mouth pressure signal through a second-order low pass filter with a time constant of 20 s. All signals (time, volume, pressure) were recorded on a strip chart (Gould Instruments, Ballain Villiers, France).

Table 1. – Anthropometric and clinical data for controls and patients with myasthenia gravis (MG)

	Age yrs	Sex M/F	Height cm	Weight kg	Duration of MG yrs	Osserman classification			
						I	IIa	IIb	III
Controls	39 (15)	5/5	171 (10)	70 (13)	-	-	-	-	-
Ocular MG	44 (20)	2/2	174 (10)	80 (19)	11.3 (18.5)	4	-	-	-
General MG	46 (18)	7/6	171 (8)	76 (16)	7.3 (9.5)	-	1	9	3

Data are presented as mean, and SD in parenthesis. M: male; F: female. Osserman classification [13]: I=ocular MG; IIa=generalized mild, no crisis, good drug response; IIb=generalized moderate to severe, skeletal and bulbar involvement, no crisis, drug response limited; III=acute with respiratory crisis, poor drug response.

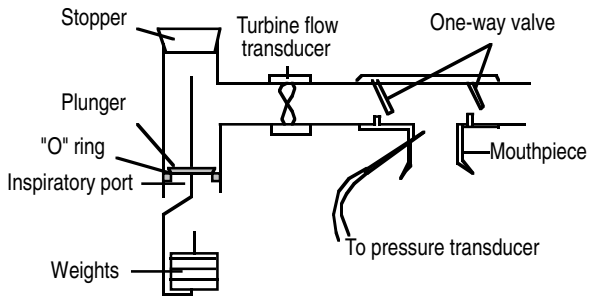

Fig. 1. – Apparatus for measuring ventilatory muscle endurance using maximal voluntary incremental threshold loading. The patient is required to generate sufficient inspiratory pressure to open the inspiratory port of the weighted plunger.

For the 2 min incremental load test, subjects began at a low load (50 g) and weights were added every 2 min until the subject could not continue. Only levels which subjects could tolerate for the full 2 min were included in the analysis. The mean mouth pressure generated over six breaths ($\bar{P}$) was recorded for each weight. The values of the maximum load achieved and the $\bar{P}$ measured at the maximum load were taken as measures of respiratory muscle endurance.

The subjects were monitored with finger pulse oximetry (Ohmeda 3700, Ohmeda Co, Boulder, CO, USA). Individuals wore noseclips and were seated upright during the test.

Protocol

The myasthenia gravis patients arrived at the pulmonary function laboratory on the morning of their study, having abstained from anticholinesterase inhibitors for at least 12 h. After obtaining informed consent, they underwent spirometry, measurements of MIP and MEP and the 2 min incremental threshold loading test. The patients then received 1 mg of neostigmine intramuscularly and rested for 20 min, following which all baseline tests with the exception of dyspnoea score were repeated.

Similarly, the controls performed spirometry, measurements of MIP and MEP and the 2 min incremental threshold loading test. They then received a placebo intramuscular injection and rested for 20 min prior to retesting.

Statistics

Group data were expressed as mean±standard deviation and range. Measurements of dyspnoea and pulmonary function before and after neostigmine (or placebo) were tested with the paired Student's t-test. The relative changes in measurements between groups were measured with the t-test for independent samples. Correlations between the various measurements in the generalized myasthenia gravis group were examined using the Pearson correlation matrix.

Results

The dyspnoea index at baseline was significantly less for the generalized myasthenia patient group (7.9±1.4) than for the control group (10.2±1.5) ($p<0.03$) or the ocular myasthenia patient group (11.0±1.4) ($p<0.02$). Hence, generalized myasthenia gravis patients were more dyspnoeic than the other two groups. There was no difference in the dyspnoea scores of the ocular myasthenia group compared to the control group.

Whilst the baseline spirometry of the generalized myasthenia gravis group revealed a lower FVC and FEV_1 than the control and ocular myasthenia gravis groups, the differences did not achieve statistical significance (table 2). The ratio of FEV_1/FVC was normal in all groups. After injection of neostigmine in the two myasthenia gravis groups and placebo in the control group, there was no significant change in FVC and FEV_1 (table 2).

The baseline MIPs and MEPs of the generalized myasthenia gravis group were lower than either the control group ($p<0.004$ and $p<0.003$, respectively) or ocular myasthenia group ($p<0.003$ and $p<0.03$, respectively) (table 3), but were not different between the ocular myasthenia patients and controls. After neostigmine, the MIP increased significantly ($p<0.03$) in the generalized myasthenia group, but not in the control or ocular myasthenia groups. MEP did not increase significantly from baseline in any of the three groups. However, there was a trend towards a greater relative increase in MEP in the generalized myasthenic group (17% increase) compared with the control group (1% decrease) ($p=0.095$).

In patients with generalized myasthenia gravis, the effect of neostigmine on ventilatory muscle strength may

Table 2. – Spirometric measurements pre- and post-neostigmine in controls and patients with ocular and generalized myasthenia gravis (MG)

	FVC				FEV_1			
	Pre		Post		Pre		Post	
	L	% pred	L	% pred	L	% pred	L	% pred
Controls	4.2	94	4.1	92	3.5	100	3.4	98
	(0.8)	(13)	(0.8)	(15)	(0.7)	(13)	(0.7)	(15)
Ocular MG	4.4	98	4.3	96	3.4	105	3.3	100
	(1.4)	(14)	(1.4)	(15)	(1.5)	(20)	(1.4)	(19)
Generalized MG	3.4	83	3.5	85	2.8	88	2.9	89
	(0.6)	(17)	(0.7)	(17)	(0.5)	(20)	(0.7)	(19)

Data are presented as mean, and SD in parenthesis. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value.

Table 3. – Comparison of maximal inspiratory (MIP) and expiratory (MEP) pressures pre- and post-neostigmine between controls and patients with ocular and generalized myasthenia gravis (MG)

	MIP				MEP			
	Pre		Post		Pre		Post	
	cmH_2O	% pred	cmH_2O	%pred	cmH_2O	% pred	cmH_2O	%pred
Controls	109	105	114	110	145	78	144	77
	(22)	(22)	(24)	(22)	(53)	(13)	(53)	(8)
Ocular MG	109	97	118	105	207	99	181	87
	(14)	(5)	(20)	(10)	(66)	(32)	(58)	(27)
Generalized MG	67	70*	80	83***	86	50**	101	59
	(26)	(28)	(26)	(29)	(38)	(25)	(42)	(25)

Data are presented as mean, and SD in parenthesis. % pred: percentage of predicted value. *: p<0.004 *vs* pre controls, p<0.003 *vs* ocular MG pre; **: p<0.003 *vs* pre controls, p<0.03 *vs* ocular MG pre; ***: p<0.03 *vs* generalized MG pre.

be related to the degree of weakness. Only one of four patients with a MIP greater than 80% predicted (*i.e.* normal) increased their MIP by greater than 10% following neostigmine, while five of the nine patients with MIPs less than 80% predicted increased by this amount.

There was no consistent relationship between the effect of neostigmine on the inspiratory and expiratory muscles in patients with generalized myasthenia gravis. (ΔMIP *vs* ΔMEP; r=0.34; p=0.12). The generalized myasthenia gravis group reached a smaller load (p<0.0005) and had a lower $\bar{P}$ (p<0.03) during the incremental threshold loading test than the controls. There was no difference in endurance between the control group and patients with ocular myasthenia gravis (table 4). We found no change in the mean values of ventilatory muscle endurance after neostigmine (table 4) in any of the three groups.

The effect of neostigmine on ventilatory muscle endurance varied among patients with generalized myasthenia gravis (fig. 2). Overall, there was no significant change in $\bar{P}$ or peak load achieved on incremental threshold loading after neostigmine. Considerable interindividual heterogeneity of response was evident, however. There was a significant relationship between the change in maximal inspiratory pressure and change in endurance after neostigmine (fig. 2) (r=0.68; p<0.05). The patients, therefore, showing an improvement in maximal static pressures in response to cholinesterase inhibitors were generally those who had an improvement in measures of ventilatory muscle endurance. Those patients whose MIP was >80% predicted did not show an improvement in $\bar{P}$ on peak load after neostigmine.

Table 4. – Comparison of maximal load and $\bar{P}$ during incremental threshold loading pre- and post-neostigmine in controls and patients with myasthenia gravis (MG)

	Load g		$\bar{P}$ cmH_2O	
	Pre	Post	Pre	Post
Controls	580	620	31.1	30.5
	(155)	(155)	(8.0)	(7.9)
Ocular MG	400	450	29.3	32.8
	(87)	(58)	(2.9)	(5.0)
Generalized MG	246*	258	19.4**	18.9
	(166)	(132)	(14.9)	(10.3)

Data are presented as mean, and SD in parenthesis. *: p<0.0005 *vs* pre controls; **: p<0.03 *vs* pre controls.

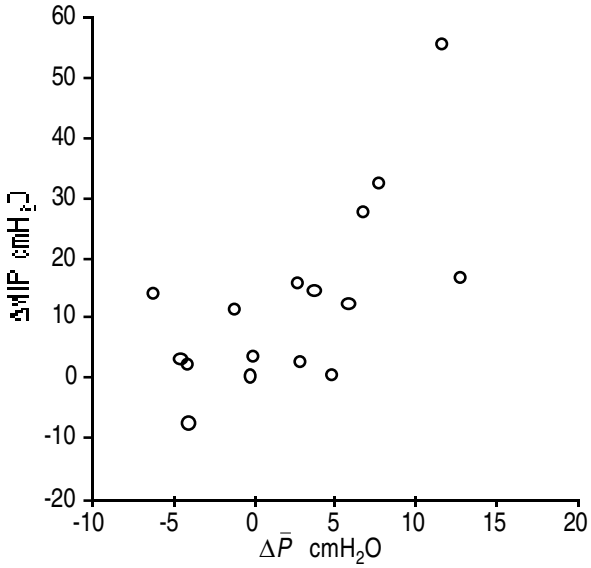

Fig. 2. – Comparison of the change in maximal inspiratory pressure (MIP) *versus* the change in mean mouth pressure ($\bar{P}$) at maximal load during incremental threshold loading with neostigmine (after-before).

The dyspnoea score correlated well with FVC in the generalized myasthenia gravis patients (r=0.663; p<0.02) but not with measures of ventilatory muscle strength or endurance, although there was a trend toward a positive relationship with $\bar{P}$. The FVC correlated well with the MEP (r=0.649; p<0.02) and the $\bar{P}$ (r=0.627; p<0.03) but not with MIP or load achieved.

Discussion

In this study, we found that patients with ocular myasthenia gravis did not differ from normal controls either in their grading of dyspnoea or their measures of spirometry, ventilatory muscle strength or endurance. On the other hand, patients with generalized myasthenia gravis were significantly more dyspnoeic than controls and had decreased ventilatory muscle strength and endurance. After administration of neostigmine, there was no improvement in ventilatory muscle strength or endurance in the

patients with ocular myasthenia gravis. Whereas, the patients with generalized myasthenia gravis demonstrated an increase in ventilatory muscle strength (at least of the inspiratory muscles) after neostigmine, as a group the measure of ventilatory muscle endurance did not improve.

Whether myasthenia gravis patients with clinically apparent ocular involvement only have subclinical involvement of ventilatory muscles, has not been established. Previous studies of pulmonary function and ventilatory muscle strength and endurance have focused on patients with generalized myasthenia gravis [1–6]. In our group of four patients with clinical ocular myasthenia gravis, there was no evidence of ventilatory muscle involvement. Given the recognized limitations in sensitivity of standard tests of ventilatory function, we cannot conclude with certainty that the ventilatory muscles are not involved to a limited degree in patients with clinically isolated ocular myasthenia gravis. However, from our findings, we would suggest that in patients with myasthenia gravis clinically restricted to ocular muscles, ventilatory muscle involvement would not be of clinical significance.

Many patients with myasthenia gravis have a restrictive pattern on pulmonary function testing and evidence of ventilatory muscle weakness. In our study, the generalized myasthenia gravis patients as a group had a lower FVC compared with the control and ocular myasthenia gravis groups, though this difference did not reach significance. Our mean FVC was similar to the value for vital capacity (VC) (85%) found by RADWAN *et al.* [6], but greater than that found by others [1, 3, 5]. The discrepancies between these studies probably reflect differences in the degree of involvement of the ventilatory muscles in the different patient populations studied. In our study, the mean MIP of patients with generalized myasthenia gravis was 67 cmH_2O (70% pred) similar to that reported previously [1, 4–6].

After administration of neostigmine, there was no appreciable increase in the FVC of any group. Whilst our results are consistent with those of MIER-JEDREZEJOWICZ *et al.* [5], three other studies have demonstrated an increase in FVC after cholinesterase inhibitors [2, 3, 6]. One of these studies did not have a control group [6], and another was composed of patients with more severe involvement of their ventilatory muscles (mean VC of 67% pred) [3]. As our patients had a higher baseline mean FVC than most other studies, one would expect that improvement would be more difficult to demonstrate. A larger patient group, lending greater power, may have demonstrated a significant increase after neostigmine.

Ventilatory muscle endurance was reduced in our patients with generalized myasthenia gravis. In patients with ventilatory muscle weakness, one would assume that a decrease in endurance would be attributable to a decrease in ventilatory muscle strength. Our study supports this assumption by showing a strong correlation between MIP and both P and load achieved.

Two previous studies have examined the effect of cholinesterase inhibitors on ventilatory muscle endurance. RADWAN *et al.* [6] measured maximum voluntary ventilation (MVV) over a 30 s period as an approximate index of respiratory endurance, and found it to be decreased (48% pred) in their patients with myasthenia gravis. After 0.5 mg of neostigmine, the MVV increased significantly from baseline. Unfortunately, this study did not have a control group, making interpretation of these results difficult. RENZI *et al.* [4] measured ventilatory muscle endurance using a 15 s sustained maximal inspiratory effort before and after prostigmine. Endurance was defined as the rate of force loss over time. They concluded that, whilst prostigmine improved muscle strength, it only partially restored endurance. Similarly, we have demonstrated an increase in ventilatory muscle strength without appreciable change in endurance.

One would expect that patients with myasthenia gravis would demonstrate an increase in ventilatory muscle endurance following a cholinesterase inhibitor. However, we observed appreciable interpatient variability in response to neostigmine, such that important patterns of response may have been masked by examining only mean changes in strength and endurance. Within our generalized myasthenia patients, several different patterns of response were identified. Four patients appeared to have relative sparing of their ventilatory muscles, with MIP levels greater than or equal to 80% predicted, and a $\bar{P}$ within the normal range (generalized myasthenia gravis, normal ventilatory muscles). This group did not respond to neostigmine. Of the remaining nine patients, four showed proportionate increases in ventilatory muscle strength and endurance (abnormal ventilatory muscles, neostigmine responsive). Finally, five patients did not respond consistently to neostigmine, (abnormal ventilatory muscles, neostigmine unresponsive).

There are several possible explanations for the lack of improvement in strength and endurance in some patients following neostigmine. Firstly, a reduction of acetylcholine receptor density in patients with severe myasthenia gravis may prevent any improvement despite the availability of greater concentrations of acetylcholine at the neuromuscular junction. Secondly, the effect of neostigmine may vary from patient to patient due to varying levels of antibody or affinity for the postsynaptic receptors, requiring greater amounts in some patients for similar clinical effects. Thirdly, the amount of neostigmine necessary to produce an improvement in one sustained contraction may be insufficient to improve measures of repetitive contraction. A further consideration would be the presence of muscle weakness unrelated to neuromuscular blockade in our patients with myasthenia gravis. The majority of patients had disease of prolonged duration, with the possibility of muscle atrophy. Furthermore, a number of patients received chronic doses of corticosteroids recognized to cause a myopathy [17].

Tests of ventilatory muscle strength are more sensitive than routine spirometry in detecting ventilatory muscle involvement in patients with myasthenia gravis. Since myasthenia gravis is characterized by fatiguability, one would expect that tests of ventilatory muscle endurance would be even more sensitive. However, in this study, only patients with abnormal MIPs were found

to have decreased ventilatory muscle endurance, as measured by the incremental threshold loading test. We conclude, therefore, that this measure of endurance adds no further useful information to tests of ventilatory muscle strength in patients with generalized myasthenia gravis.

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