Pulmonary Function Testing in Elderly Patients Treated for a Myasthenia Gravis Exacerbation

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Abstract

Background and Purpose: Pulmonary function testing is a standard part of care for patients admitted to hospital with a myasthenia gravis exacerbation. It may inform clinicians' decisions to intubate patients. It is known that pulmonary function declines with age in healthy adults. We studied the effect of age on pulmonary function and serious respiratory events, including intubation, in patients admitted to hospital for a myasthenia gravis exacerbation. **Methods:** Single center, retrospective cohort of consecutive patients treated for a myasthenia gravis exacerbation. Demographics, pulmonary function tests (PFTs), and respiratory events requiring intubation or emergency respiratory therapy were recorded for each encounter. Relationship of PFTs to age was analyzed using age as a continuous and as a dichotomous (cut-value 70 years) variable. **Results:** Forty-nine encounters from 39 patients were included. Slow vital capacity (SVC) was negatively correlated with age (R 0.46, P value .002). Maximum inspiratory pressure (MIP) and SVC were significantly reduced in elderly versus nonelderly patients (MIP-20.0 vs -30.0 cm H₂O, P value .004; SVC 16.5 vs 23.4 mL/kg, P value .013). The incidence of respiratory events did not significantly differ between elderly and nonelderly patients (χ^2 P value .08). **Conclusions:** In patients treated for a myasthenia gravis exacerbation, pulmonary function values are significantly reduced in elderly patients compared to nonelderly patients. Despite very low SVC and MIP values most elderly patients do not require intubation however they do require intensive monitoring for serious respiratory complications.

Keywords

myasthenia gravis, myasthenia gravis exacerbation, pulmonary function tests, elderly, vital capacity, age effects

Introduction

The most serious complication of myasthenia gravis is respiratory failure. Patients with exacerbations of myasthenia gravis are frequently admitted to hospital for careful monitoring with the goal of intubating patients with respiratory failure prior to the need for emergency intubation. Pulmonary function testing using spirometry is routinely performed to monitor respiratory status. A vital capacity (VC) of 15 to 20 mL/kg or a maximal inspiratory pressure (MIP) less negative than -25 to -30 cm H₂O is often cited as a cut-off for considering intubation in patients with myasthenia gravis.¹ However, previous studies have concluded that, in patients admitted for myasthenia gravis, MIP and VC are not predictive of the need for mechanical intervention.^{2,3}

Myasthenia gravis is a disease of older adults. The mean age of presentation is 60 years old and incidence rates increase with age.⁴ Lung function declines with age, for example, the

MIP for healthy adult males declines from -84 to -56 cm H₂O between the age of 65 and 85 years.⁵ Approximately 1/4 of the forced vital capacity is lost from age 20 to 80.⁶ Whether this age-related decrement in lung function places in elderly patients at greater risk for respiratory complications is unstudied, but intuitively this seems likely. It is also unclear whether

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the interpretation of pulmonary function tests should account for this age-related decrement.

In this study, we sought to determine the relationship between age and respiratory function in patients admitted with myasthenia gravis. We hypothesized that elderly patients would have greater impairment of lung function as measured by spirometry and would be more likely to suffer respiratory complications including intubation.

Methods

Study Design

Retrospective cohort of patient encounters for acute exacerbations of myasthenia gravis. Ethics approval was granted by the Ottawa Hospital Research Institute—Research Ethics Board. A waiver of informed consent was granted.

Patients

Eligible encounters were identified using structured discharge abstracts from the Ottawa Hospital. Inclusion criteria were: (1) primary or secondary discharge diagnosis of myasthenia gravis, (2) age ≥ 18 years, and (3) encounter discharge date between April 30, 2010, and January 31, 2015. Encounters were excluded if chart review failed to substantiate occurrence of exacerbation (eg, absence of rescue therapy), mechanical ventilation was instituted prior to arrival to hospital, or mechanical ventilation was instituted due to primary pulmonary disease such as pneumonia rather than neuromuscular weakness.

Management Protocols

Each patient was managed per an individualized plan of care, under the admitting or consulting care of a neurologist. Typically, patients were monitored with continuous telemetry and pulse oximetry and frequent (min Q4H-Q6H) vital signs and pulmonary function tests (PFTs). Patients requiring assisted ventilation were transferred to the care of a critical care specialist. Pulmonary function tests were performed by registered respiratory therapists, relying on the best of 3 measurements performed in the semi-Fowler or sitting position. Facial masks were used for patients with facial weakness. Slow vital capacity (SVC), MIP, and maximum expiratory pressure (MEP) were recorded for each PFT. Initiation and termination of ventilator support were at the discretion of the treating neurologist and critical care specialist, generally based on clinical assessment.

Chart Review

One author (S.V.G.) reviewed all charts, extracting data using a standardized template coded in Microsoft Access 2010 (Microsoft, Seattle, Washington). Patient-level variables included: sex, weight, serology, and cardiopulmonary

Table 1. Reason for Exclusion of Encounters With Primary or Secondary Diagnosis of Myasthenia Gravis.

Reason For Exclusion	Number
Diagnosis of myasthenia gravis not substantiated on follow-up	8
No rescue therapy with IVIG or plasmapheresis (stable disease)	94
Maintenance IVIG or plasmapheresis without evidence of exacerbation	13
Rescue IVIG or plasmapheresis without evidence of exacerbation	5
Intubation prior to arrival at hospital	2
Overwhelming pulmonary disease (pneumonia)	1
Inadequate documentation of encounter	1

Abbreviation: IVIG, intravenous immunoglobulin.

comorbidities. Encounter-level variables included: age, admission examination findings, preadmission therapy, discharge disposition, and occurrence of respiratory events (either mechanical ventilation or decompensation requiring emergency respiratory therapy services). All PFTs and vital signs were recorded for each encounter. Data collection ceased at the first respiratory event, death, discharge, institution of palliative care measures, or designation as “alternate level of care” (indicating patient is stable for transfer to rehabilitation or a skilled nursing facility, pending an available bed).

Data Analysis

Patients and encounters were grouped by age as elderly (≥ 70 years) or nonelderly (< 70 years). Patients with multiple encounters were categorized based on age at their first encounter. Categorical variables were described by count or proportion, using χ^2 for tests of between-group difference. Distribution of interval variables was visually assessed by histogram and using the Shapiro-Wilk test (P value threshold .1). Normally and nonnormally distributed variables were respectively described by mean and standard deviation or by median and range and compared by the Student t test or the Mann-Whitney U-test. Slow vital capacity was correlated with age using the Pearson correlation.

Analysis was performed using R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) implemented in R Studio 0.99.896 (RStudio, Inc., Boston, Massachusetts), with the following packages (versions in parentheses): dplyr (0.4.3), ggplot2 (2.1.0), xlsx (0.5.7), psych (1.6.4), and tables (0.7.79).

Results

A primary or secondary diagnosis of myasthenia gravis was recorded in 173 inpatient encounters during the study period. Of these, 49 encounters from 39 patients met our eligibility

Table 2. Characteristics of Patients and Encounters, Grouped by Age at First Encounter. Except Where Noted, All Figures Refer to Count (Column Percent).^a

Patient-level Variables	Age < 70 years (N = 15)	Age ≥ 70 years (N = 24)	P Value
Female sex	10 (67%)	9 (38%)	.149
Pulmonary/cardiac comorbidity	4 (27%)	11 (46%)	.391
Diagnosis during first encounter	5 (33%)	8 (33%)	1.000
More than one encounter	3 (20%)	6 (25%)	.720
Serology			.224
Acetylcholine receptor Antibodies	12 (80%)	23 (96%)	
MuSK Antibodies	1 (7%)	0	
Seronegative	1 (7%)	1 (4%)	
Not tested	1 (7%)	0	
Encounter-level Variables	Age < 70 years (N = 18)	Age ≥ 70 years (N = 31)	P Value
Intubation	1 (6%)	8 (26%)	.170
Any respiratory event (incl. intubation)	2 (11%)	12 (39%)	.083
Feeding tube placed	2 (11%)	12 (39%)	.083
Median acute care length of stay (interquartile range)	5.8 (5.2-6.6)	11.5 (7.5-21.5)	.001
Preadmission immune therapy	11 (61%)	15 (48%)	.573
Initial exam – bulbar signs	17 (94%)	24 (77%)	.249
Initial exam – respiratory signs	1 (6%)	12 (39%)	.028
Treatment – IVIG	12 (67%)	24 (77%)	.623
Treatment – Plasmapheresis	7 (39%)	6 (19%)	.247
Disposition			.079
Home	16 (89%)	17 (55%)	
Acute care	1 (6%)	2 (6%)	
Continuing care	1 (6%)	9 (29%)	
Death	0	3 (10%)	

Abbreviations: ACRA, acetylcholine receptor antibody; IVIG, intravenous immune globulin; MuSK, muscle specific kinase.

^aP values refer to χ^2 (categorical) or Mann-Whitney U (interval).

criteria and were included in the analysis. Reasons for exclusion are listed in Table 1.

Median age at first encounter in this cohort was 75 years; 26 patients were aged 70 years or greater at the time of the first encounter (elderly cohort). Characteristics of included patients and encounters are presented in Table 2, grouped by age. Eight of 31 (26%) of elderly patient encounters and 1 of 18 (6%) of nonelderly patient encounters involved intubation ($P = .170$). Of the 9 patients that were intubated, 3 had no PFTs during the hospital admission, and 2 other patients had not had PFTs performed within 12 hours of the intubation. Serious respiratory events occurred during encounters from 12 (39%) of 31 of elderly and 2 (11%) of 18 of nonelderly patients ($P = .08$). Details of the respiratory encounters are described in Table 3. The median acute care length of stay was 11.5 days in the elderly group and 5.8 days in the nonelderly group ($P = .001$).

A total of 586 PFTs were recorded, 56 (9.5%) of which were missing either SVC or MIP/MEP. At least one PFT was recorded for 43 of 49 encounters. Results of pulmonary function tests by age are summarized in Table 4 (nadir values for SVC, MIP, MEP) and Figure 1 (range and final value for SVC). Values for nadir SVC and MIP were significantly reduced in elderly versus nonelderly patients (SVC 16.5 vs 23.4 mL/kg, $P = .013$, MIP -20.0 vs -30.0 cm H₂O,

$P = .004$). Final value for SVC was negatively correlated with age ($R = -0.46$, $P = .002$). Slow vital capacity nadir < 20 mL/kg was observed in 18 (72%) of 25 patients aged > 70 years, and 7 (41%) of 17 patients aged < 70 years (one patient aged < 70 had no valid SVC measurements).

Discussion

In this study of 49 patient encounters for myasthenia gravis exacerbation, we document a significant reduction in nadir SVC (mL), in nadir SVC (mL/kg), and in nadir MIP in patients >70 years old compared to patients <70 years old. This is the first study that has demonstrated the extent of the decline of pulmonary function with age in patients admitted for an exacerbation of myasthenia gravis. The slope of the decline of vital capacity with age in our study group visually parallels the slope of decline with age in gender-matched, healthy controls. Although the rate of decline with age is similar, the absolute value of vital capacity prior to discontinuation of monitoring with spirometry was reduced by approximately 1 L in women and 1.5 L in men compared to gender-matched healthy controls. Therefore, the effect of age and myasthenia gravis on respiratory function appears to be additive. This is important to recognize because lower values on the pulmonary function tests are described as a factor

Table 3. Description of Serious Respiratory Events.

Age	Time From Admission (h)	Summary of Event	Time From Last PFT (h)	MIP (cm H ₂ O)	MEP (cm H ₂ O)	SVC (mL/kg)
29	21	Hypoxemia followed by apnea requiring emergency intubation. Gentamicin 90 mg IV given 40 minutes prior to onset of respiratory failure.	6	−40	30	18.15
60	89	Three emergency calls to respiratory therapy for dyspnea with signs of fatigue including shallow breathing and accessory muscle use. Prednisone 30 mg/d started 3 days prior to first event.	1	−30	30	No SVC
74	8	Persistent desaturation following attempted placement of feeding tube, leading to intubation within 90 minutes. No identifiable trigger. No pneumothorax.	No pulmonary function tests			
74	5	Three episodes of desaturation treated with high flow oxygen (non-rebreather and high-flow nasal accumulator). Intubation 2 days later for presumed hypercarbic respiratory failure (rapidly reversible coma).	No pulmonary function tests			
75	0.5	Hypoxemic respiratory distress culminating in respiratory failure and intubation after trial of nonrebreather mask. No identifiable precipitant.	No pulmonary function tests			
76	117	Dyspnea progressing to hypercarbic/hypoxemic respiratory failure; patient intubated approximately 2 hours after first emergency call to respiratory therapy. Prednisone 40 mg/d started 4 days prior to event.	13	−30	60	10.00
81	30	Resting hypoxemia worsening over 1 hour, initially requiring 3 L NP but quickly changed to NRB. Transferred to ICU, but did not require intubation. No identifiable trigger.	2	−20	25	19.28
83	145	Hypoxemic respiratory failure culminating in emergency intubation after trial of nonrebreather mask. No identifiable precipitant.	69	−30	70	20.78
83	16	Hypoxemia treated with oxygen by high flow nasal accumulator.	No pulmonary function tests			
84	35	Hypercarbic respiratory failure leading to apnea and emergency intubation. Intravenous infusion of magnesium 5 g started prior to onset of respiratory distress.	3	−8	10	21.88
85	2	Six episodes of desaturation each requiring emergency respiratory therapy. Transferred to ICU for bronchoscopy and pulmonary toilet, but not intubated. Several episodes treated with nonrebreather mask. No identifiable trigger.	No pulmonary function tests			
85	86	Seven episodes of desaturation leading to emergency calls for respiratory therapy. Transient use of face mask with high oxygen flow rates (nonrebreather or Venturi at 60%). No identifiable trigger.	No pulmonary function tests			
89	76	Elective intubation on third day of admission after poor performance on pulmonary function test. No identifiable trigger.	0.3	−10	10	15.57
89	25	Urgent intubation with hypercapnea and depressed level of consciousness but normal vital signs.	5	−20	25	7.41

Abbreviations: MIP, mean inspiratory pressure; MEP, mean expiratory pressure; PFT, pulmonary function test; SVC, slow vital capacity.

Table 4. Nadir Values for Pulmonary Function Tests, Grouped by Age.^a

Respiratory Parameter	Age < 70 years (N = 18)	Age ≥ 70 years (N = 25)	P Value
Tests per encounter	11 (10-16)	13 (7-21)	
Nadir SVC (mL/kg)	23.4 (8.9)	16.5 (7.6)	.013
Nadir SVC (mL)	1786 (742)	1233 (673)	.019
Nadir MIP (cm H ₂ O)	−30.0 (−25-45)	−20.0 (−10 to 25)	.004
Nadir MEP (cm H ₂ O)	32.5 (−40 to 20)	32.5 (20-40)	.230

Abbreviations: MIP, maximal inspiratory pressure; MEP, maximum expiratory pressure; SVC, slow vital capacity

^aValues displayed are median (interquartile range) for tests per encounter, MIP and MEP, and mean (standard deviation) for SVC (mL) and SVC (mL/kg) which are normally distributed. P values refer to Mann-Whitney U (MIP, MEP) or t test (SVC [mL] and SVC [mL/kg]).

which physicians should consider when deciding whether to intubate patients.

In our cohort, there was no significant difference in the rate of intubation in the older group despite lower PFT values. Similarly, in their study, Thieben et al³ found no significant difference in age between the myasthenic patients who were intubated versus those who were not. The low rate of intubation despite the very low PFT values suggests that our institution does not emphasize those values when deciding when to intubate. This conclusion is supported by the fact that over half of the patients that were intubated had no recorded PFT within 12 hours of the intubation.

Intubation of elderly patients with myasthenia gravis is not without risk. Age over 50 years is a risk factor for prolonged

Figure 1. Range (vertical bar) and Final Value (dot) of slow vital capacity (mL) in female and male patients with myasthenia gravis. The solid line demonstrates the linear relationship between age and the final value of slow vital capacity. The dashed line represents values from a population sample of healthy controls.⁷

intubation in myasthenic crisis.⁷ Increased time on mechanical ventilation is associated with atelectasis, *Clostridium difficile* infection, anemia, and congestive heart failure in patients with myasthenia gravis.⁷ Prolonged intubation is also closely associated with poor functional outcome after myasthenic crisis.⁷ Our data show that many older people can be supported without ultimately requiring intubation, and being subjected to those risks.

Although there was no statistically significant difference in the rate of intubation in elderly patients, there are several indicators that this group of patients requires close monitoring and intensive medical care. There was a trend to both an increased rate of respiratory events and feeding tube placement in the patients >70 years old. The patients >70 years old spent significantly more days in an acute care setting. In addition, there were 3 acute-care deaths in the group >70 years old compared to no deaths in the group <70 years old, although none were due to acute respiratory failure. To mitigate the risk of sudden respiratory decompensation that remains if tenuous patients are not intubated, it is important that they be monitored closely in a setting where emergency intubation can be performed if necessary.

The principal strength of this study is our robust ascertainment of respiratory events. First, as all but one patient was intubated in the setting of severe clinical respiratory

decompensation, we are confident that unnecessary intubations did not confound the number of serious respiratory events recorded. Second, we expanded the definition of serious events beyond the institution of mechanical ventilation. Several of our patients experienced serious respiratory compromise (eg, mucous plugging) that did not require ventilation but that might have been fatal without close monitoring.

The main limitation of this study is the small sample size. The small sample precluded the use of multivariable analytic techniques. As it is a retrospective study, it is possible that there are confounding variables that are not controlled. Replication in a large, multicenter sample is desirable.

In conclusion, in patients treated for a myasthenia gravis exacerbation, pulmonary function test values are significantly reduced in elderly patients compared to nonelderly patients. Despite very low SVC and MIP values, most elderly patients do not require intubation however they do require intensive monitoring for serious respiratory complications.

Declaration of Conflicting Interests

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References

1. Bird SJ, Levine JM. *Myasthenic exacerbation*. In: Shefner JM, Targoff IN, Parsons PE, Echler AF, Findlay G, eds. *Uptodate*. Waltham, MA: Uptodate; 2018.
2. Rieder P, Louis M, Joliet P, Chevrolet JC. The repeated measurement of vital capacity is a poor predictor of the need for mechanical ventilation in myasthenia gravis. *Intensive Care Med*. 1995; 21(8):663-668.
3. Thieben MJ, Blacker DJ, Liu PY, Harper CM, Wijdicks EFM. Pulmonary function tests and blood gases in worsening myasthenia gravis. *Muscle Nerve*. 2005;32(5):664-667.
4. Breiner A, Widdifield J, Katzberg HD, Barnett C, Bril V, Tu K. Epidemiology of myasthenia gravis in Ontario, Canada. *Neuromuscular Disord*. 2016;26(1):41-46.
5. Janssens JP. Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. *Clin Chest Med*. 2005;26:469-484.
6. Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med*. 2008;177(3):253-260.
7. Thomas CE, Mayer SA, Gungor Y, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. *Neurology*. 1997;48(5):1253-1260.