Timing of Decremental Response During Repetitive Nerve Stimulation in Myasthenia Gravis

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ABSTRACT

Introduction: A decrement >10% detected during repetitive nerve stimulation (RNS) is supportive of considering a diagnosis of myasthenia gravis (MG). Several studies have found that most of this decrement is seen between 4 to 6 min post-exercise. However, there is limited literature looking at whether shorter timing and lower cuttoff would be sufficient. This study aimed to evaluate if RNS up to 2 min post-exercise is adequate to detect a decrement response > 10% as well as calculate sensitivities and specificities using different cutoff values (>9%, >8%, >7%, and >6%) for abnormal decrement. **Methods:** A retrospective review of RNS and serology data between 2013 to 2017 in patients with and without MG was performed at The University of Kansas Medical Center. According to positive serology and electrodiagnostic testing, patients were divided into control and MG groups. **Results:** 76 patients with MG and 100 controls were identified. An abnormal decrement was detected in 95% of MG patients within 2 min post-exercise. Also, using cutoff values ≥ 9% on facial and accessory nerves and ≥ 7% on the ulnar nerve maintained specificities ≥95%, and sensitivities increased from 30% to 37%, 36% to 62%, and 21% to 41%, respectively. *Conclusions:* RNS up to 2 min post-exercise might be sufficient to detect a significant decrement in MG patients. Also, lowering cutoff values increases RNS sensitivity, maintaining or slightly decreasing specificity.

Keywords: *Myasthenia gravis, Decrement, Repetitive nerve stimulation, Sensitivity, Specificity*

Introduction

Repetitive nerve stimulation (RNS) and single-fiber electromyography (SFEMG) are electrodiagnostic testings used for the evaluation of myasthenia gravis (MG) (1). SFEMG is the most sensitive test for the assessment of suspected MG cases, but RNS is used more widely due to its availability, rapidity, non-invasive nature, and high specificity (>95%) (2, 3).

RNS comprises 5 to 10 trains of supramaximal stimuli at low frequencies (2–3 Hz) during the recording of compound muscle action potentials (CMAPs) at baseline, immediately after 60 s of exercise, and at 1, 2, 4, and 6 min post-exercise. A decrement >10% at any stimuli has been considered positive to diagnose neuromuscular-junction disorders, including MG. Several studies have suggested an evaluation of up to 6 min because the most significant decrement is seen between 2 to 4 min after exercise (4). However, studies looking at whether shorter timing would provide identical information are lacking.

The sensitivity of RNS varies according to MG severity, muscle tested, and cutoff values used (5, 6). Some studies have been performed to propose "ideal" cutoff values. Still, many of them have failed due to small sample sizes or technical issues that have restricted the analyses of electrodiagnostic data (7). Historically, most neuromuscular teams have set up a decrement >10% as a cutoff for MG (3). Nevertheless, a lower cutoff could be used due to the precision of modern equipment, according to other studies (8, 9).

This study aimed to ascertain if RNS up to 2 min post-exercise is sufficient to detect an abnormal decrement in MG patients. We also aimed to determine different sensitivities and specificities when the cutoff is lowered (9% to 6%) in commonly tested nerves.

Methods

After obtaining IRB approval, a retrospective chart review of patients referred for evaluation of symptoms suggestive of MG was carried out at the University of Kansas Medical Center from January 2013 to September 2017. Patients were identified from a database of neuromuscular diseases using the tenth revision of the International Statistical Classification of Diseases and MUS-codes. Demographic, clinical, serologic, and electrodiagnostic information was extracted. RNS was obtained in all these patients and was performed by either two of our EMG technicians. Also, some of them underwent SFEMG according to each clinician's criteria and were performed by the same neuromuscular specialist, including the interpretation of the results. Patients with symptoms suggestive of MG with either + AChRAb, + muscle-specific kinase - MuSK, or + low-density lipoprotein receptor-related protein 4 - LRP4, + RNS, or + SFEMG were assigned to the MG group. These patients were further divided into ocular MG (OMG) and generalized MG (GMG) if weakness involved only ocular muscles or other muscle groups. Patients with both negative serology and electrodiagnostic testing (RNS and SFEMG) were included in the control group.

Standard testing methods were used during RNS evaluation in our center (4). Five to ten trains of supramaximal stimuli at a rate of 3 Hz were applied to facial, ulnar, and accessory nerves after placing an active surface electrode (E1) on the belly of the assessed muscle and referential electrode (E2) over the tendon of the same muscle. Stimulation was applied while recording CMAPs at rest, immediately after 60 s of exercise, and then at 1, 2, 4, and 6 min post-exercise (4, 10). An abnormal RNS result was considered when the amplitude between the fifth stimulus compared with the first stimulus exhibited a decrement greater than 10% (4).

We analyzed the timing of significant decrement after RNS overall and across facial, ulnar, and accessory nerves. In addition, we calculated the sensitivities and specificities using abnormal decrement cutoff values of 9%, 8%, 7%, and 6% for facial, ulnar, and accessory nerves in MG, OMG, and GMG groups at baseline and pre/post-exercise.

Statistical analysis was performed using Microsoft Excel 2016 and MedCalc software 2018. Frequencies and percentages represented gender, clinical, serologic, and electrodiagnostic information in non-MG, OMG, and GMG groups. For ages, mean ± standard deviation (SD) was used. T-test and chi-square test were used to compare numerical and categorical variables, respectively, between OMG and GMG patients.

Results

One hundred and seventy-six patients were identified, of which 76 were diagnosed with MG, and 100 were assigned to the control group. Demographic data, serologic status, electrodiagnostic testing in the MG, MG subtypes, and control groups are shown in table 1.

All patients in the control group were tested for AChRAb and RNS. Sixty percent were tested for MuskAb, and 40% had SFEMG performed. The highest decrement response was ten seen in 1 patient when the accessory nerve was stimulated at 2- and 6-min post-exercise; however, SFEMG was not performed. In addition, 17 patients had a decrement response of 9, which was more prevalent when the accessory nerve was stimulated, with the earliest response at baseline in 12 patients.

Overall for MG patients, 71% (54 patients) were positive for AChRAb, 51% (39 patients) had abnormal RNS, and 17 out of 19 had abnormal SFEMG. In the patients with abnormal SFEMG, 5 had abnormal RNS. One was seropositive with decremental response <7% in the facial nerve. The remaining patients, eleven, were seronegative with normal RNS. Conversely, the two patients with normal SFEMG had decremental response >10%, and one of them was also seropositive. Twenty patients with OMG and 48 with GMG were identified. Age (56 ± 14.4 *vs.* 63 ± 13 years) and gender (57% *vs.* 32% women; 43% *vs.* 67% men) differences were seen in the MG vs. control group. The presence of AChRAb between OMG and GMG was statistically significant (54% *vs.* 81%; p=0.0129).

For OMG patients, 54% had abnormal RNS and 54% were positive for AChRAb, with overlapping results in 36%. One patient was positive for LRP4 with negative RNS and SFEMG. SFEMG was abnormal in 10 out of 11 patients. For GMG patients, 50% had abnormal RNS, and 81% had positive AChRAb with overlapping results in 40%. One patient who was positive for MuSK had abnormal RNS. Seven out of 8 patients had abnormal SFEMG, and two had

Table 1. Demographic, clinical, serologic, and electrodiagnostic information of MG, MG subtypes, and control groups

	Control (n=100)	MG (n=76)	OMG (*n = 28*)	GMG (*n = 48*)	*P*-value
Age	51.85 ± 14	61.44 ± 15	63 ± 13	61 ± 16	0.521
Women	56 (56%)	25 (33%)	6 (21%)	19 (40%)	0.0914
Men	44 (44%)	51 (67%)	22 (79%)	29 (60%)	0.0914
Ocular Symptoms	NA	NA	28 (100%)	44 (92%)	0.1271
Generalized Symptoms	NA	NA	NA	48 (100%)	NA
AChRAb	0/100	54/76 (71%)	15/28(54%)	39/48 (81%)	0.0129
RNS	0/100	39/76 (51%)	15/28 (54%)	24/48 (50%)	0.7381
SFEMG	0/39	17/19 (89%)	10/11 (91%)	7/8 (88%)	0.8360

Note: NA = Not Assessed

abnormal RNS. Abnormal RNS, AChRAb, and SFEMG were not seen simultaneously in OMG and GMG groups.

The prevalence of significant decrement obtained for stimulation of facial, ulnar, and accessory nerves was 24%, 25%, 28% for OMG patients and 34%, 20%, 41% for GMG patients, respectively. The first significant decrement response was detected within 2 min post-exercise in 95% (37 patients) of MG patients, and 62% (24 patients) were observed at baseline. In two patients, an abnormal response was detected after 2 min post-exercise; both cases were positive for AChRAb. The prevalence of the first significant decrement detected in MG, OMG, and GMG groups at various time points is shown in Table 2.

RNS sensitivity increased, and specificity decreased as cutoff values decreased in all the MG and MG subgroups. Using cutoff values >9% on facial and accessory nerves and >7% on the ulnar nerve maintained specificities ≥95%, and sensitivities increased from 30% to 37%, 36% to 62%, and 21% to 41%, respectively. The different sensitivities and specificities for the MG, OMG, and GMG groups using cutoff values between >10% to >6% are shown in Table 3.

Discussion

Different authors have suggested an assessment of up to 6 min during RNS based on maximal decrement as this may be seen between 2 to 4 min after exercise. This effect is called "post-exercise exhaustion" and consists of a depression in end-plate excitability after maximum voluntary contraction or tetanic stimulation (4).

Our study found that 95% of MG patients had a decremental response >10% within 2 min post-exercise. Significantly, 62% of them had this decrement pre-exercise. Only two patients had a significant decrement after 2 min post-exercise, and they both were positive for AChRAb.

Table 2. Frequencies of the first decremental response >10% seen in MG, OMG, and GMG patients

Time	Baseline	Imm. post	1 min	2 min	4 min	6 min
MG (n=39)	24(62%)	2(5%)	6(15%)	5(13%)	1(2.5%)	1 (2.5%)
OMG (n=15)						
Facial (n=6)	4 (80%)	0%	0%	2 (33%)	0 %	0%
Ulnar (n=4)	2 (50%)	0%	1 (25%)	0%	0%	1 (25%)
Accessory (n=5)	2 (40%)	0%	2 (40%)	1 (20%)	0%	0%
GMG (n=24)						
Facial (n=12)	9 (75%)	0%	2 (17%)	0%	1 (8%)	0%
Ulnar (n=8)	7 (88%)	1 (12%)	0%	0%	0%	0%
Accessory (*n=12*)	7 (58%)	1 (8%)	2 (17%)	2 (17%)	0%	0%

Table 3. RNS sensitivity and specificity using different decrement cutoff values in MG (*n* = 48), OMG (n=15), and GMG (n=33) patients

	Facial nerve		Ulnar nerve		Accessory nerve	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
>10%						
MG	30%	100%	21%	100%	36%	100%
OMG	24%	100%	25%	100%	28%	100%
GMG	34%	100%	20%	100%	41%	100%
>9%						
MG	33%	100%	25%	100%	43%	99%
OMG	32%	100%	30%	100%	33%	99%
GMG	34%	100%	22%	100%	48%	99%
>8%						
MG	37%	89%	31%	98%	62%	81%
OMG	36%	89%	35%	98%	56%	81%
GMG	37%	89%	29%	98%	66%	81%
>7%						
MG	43%	82%	33%	95%	70%	74%
OMG	40%	81%	35%	95%	67%	74%
GMG	46%	82%	32%	95%	72%	74%
>6%						
MG	52%	74%	41%	89%	77%	66%
OMG	48%	74%	40%	89%	67%	66%
GMG	54%	75%	41%	89%	83%	66%

Decrement was also seen immediately post-exercise in two patients, which is unusual. However, after reviewing the waveforms, low recruitment was noted at baseline, and decrement >10% was also present at various time points immediately post-exercise. Our findings are inconsistent with the available data in the literature, which states that the most significant decrement is detected after 2 min post-exercise (4).

In OMG patients, 100% had abnormal responses within 2 min postexercise in the facial nerve, which correlates with the involvement of ocular muscles. The prevalence of significant decrement >10% obtained for stimulation of facial, ulnar, and accessory nerves were 24%, 25%, and 28% for OMG patients, and 34%, 20%, 41% for GMG patients, with not much difference between these two MG subgroups. It is also impressive that decremental response in the ulnar nerve was higher in OMG than GMG. Unfortunately, we were unable to find studies with similar findings to compare with. We assumed that some OMG patients probably had involvement of other muscles different from the ocular ones. Still, clinical involvement may have been so mild that it was imperceptible to them, or it could be related to subtle variabilities in the RNS technique by our EMG techinicias. In addition, it is unclear why some patients with positive serology and RNS underwent SFEGM as this was decided per each clinician in our neuromuscular department.

We also calculated the sensitivities and specificities of RNS using different cutoff values. Overall, sensitivity between 30% to 80% and specificity from 90% to 100% when using a cutoff value >10% have been previously reported (5)(9). Similar findings were seen in our study except for sensitivity in the ulnar nerve, which was lower than usual, 21%. We found that sensitivity increased and specificity maintained or slightly decreased as cutoff values decreased from 10% to 6%. Similar findings were seen by *Lamb et al.* (12). The sensitivity of RNS can vary according to the distribution or severity of MG (7), and using lower cutoff values may be feasible due to better equipment precision nowadays (8). Abraham *et al.* (9) recommended an optimal cutoff value between 7% to 8% for facial stimulation because sensitivity increased, and specificity remained >90%. Similar findings were seen in our study. In MG patients, cutoff values >9% for facial and accessory nerves and >7% for ulnar nerve were associated with specificities ≥95% with increased sensitivities at these points. Looking at OMG and GMG subgroups separately, similar results were seen.

Our study has several limitations. Sampling bias may be seen due to our study's retrospective nature. Also, we did not include the severity of MG in our cohort, which might influence the sensitivities seen across the different nerves tested. A positive correlation between RNS testing and MG severity was reported previously (11). Also, the size of our cohort with abnormal RNS was small. Finally, we did not evaluate RNS according to muscle groups. Sensitivity and specificity may change according to the muscles assessed.

In conclusion, we found that 2 min of post-exercise testing could be sufficient to detect a significant decrement for MG diagnosis. We propose shorter timing for RNS testing during MG evaluation. In addition, a cutoff <10% could be used for MG evaluation. Accepting a cutoff >9% for facial and accessory nerves and >7% for the ulnar nerve maintain specificities >95% accompanied by an increment in sensitivities for MG. However, further prospective studies will be necessary to confirm our findings.

References

1. Chiou-Tan FY, Gilchrist JM. Repetitive nerve stimulation and single-fiber electromyography in the evaluation of patients with suspected myasthenia gravis or Lambert-Eaton myasthenic syndrome: Review of recent literature. Muscle Nerve. 2015;52:455-62.
2. Benatar M. A systematic review of diagnostic studies in myasthenia gravis. Neuromuscul Disord. 2006;16:459-67.
3. Medicine AQACAAoE. Literature review of the usefulness of repetitive nerve stimulation and single fiber EMG in the electrodiagnostic evaluation of patients with suspected myasthenia gravis or Lambert-Eaton myasthenic syndrome. Muscle Nerve. 2001;24:1239-47.
4. Howard JF. Electrodiagnosis of disorders of neuromuscular transmission. Phys Med Rehabil Clin N Am. 2013;24:169-92.
5. Oh SJ, Hatanaka Y, Hemmi S, Young AM, Scheufele ML, Nations SP, et al. Repetitive nerve stimulation of facial muscles in MuSK antibody-positive myasthenia gravis. Muscle Nerve. 2006;33:500-4.
6. Schady W, MacDermott N. On the choice of muscle in the electrophysiological assessment of myasthenia gravis. Electromyogr Clin Neurophysiol. 1992;32:99-102.
7. Amandusson Å, Elf K, Grindlund ME, Punga AR. Diagnostic Utility of Repetitive Nerve Stimulation in a Large Cohort of Patients With Myasthenia Gravis. J Clin Neurophysiol. 2017;34:400-7.
8. Amato A, Russell J. 2008. *Neuromuscular disorders*. McGraw Hill Professional:San Francisco.
9. Abraham A, Alabdali M, Alsulaiman A, Breiner A, Barnett C, Katzberg HD, et al. Repetitive nerve stimulation cutoff values for the diagnosis of myasthenia gravis. Muscle Nerve. 2017;55:166-70.

10. Katzberg HD, Bril V. A comparison of electrodiagnostic tests in ocular myasthenia gravis. J Clin Neuromuscul Dis. 2005;6:109-13.

11. Yan C, Song J, Pang S, Yi F, Xi J, Zhou L, et al. Palpebral portion of the orbicularis oculi muscle to repetitive nerve stimulation testing: A potential assessment indicator in patients with generalized myasthenia gravis. J Clin Neurosci. 2018;48:238-42.

12. Lamb C, Rubin D. Sensitivity and specificity of repetitive nerve stimulation with lower cutoffs for abnormal decrement in myasthenia gravis. Muscle Nerve. 2020;62:381–385.