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ARTICLE CLASS OF EVIDENCE

Repetitive ocular vestibular evoked myogenic potentials in myasthenia gravis

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Abstract

Objective
To validate the repetitive ocular vestibular evoked myogenic potentials (RoVEMP) test for diagnostic use in myasthenia gravis (MG) and to investigate its value in diagnostically challenging subgroups.

Methods
The RoVEMP test was performed in 92 patients with MG, 22 healthy controls, 33 patients with a neuromuscular disease other than MG (neuromuscular controls), 4 patients with Lambert-Eaton myasthenic syndrome, and 2 patients with congenital myasthenic syndrome.

Results
Mean decrement was significantly higher in patients with MG (28.4% ± 32.2) than in healthy controls (3.2% ± 13.9; $p < 0.001$) or neuromuscular controls (3.8% ± 26.9; $p < 0.001$). With neuromuscular controls as reference, a cutoff of ≥14.3% resulted in a sensitivity of 67% and a specificity of 82%. The sensitivity of the RoVEMP test was 80% in ocular MG and 63% in generalized MG. The RoVEMP test was positive in 6 of 7 patients with seronegative MG (SNMG) with isolated ocular weakness. Of 10 patients with SNMG with negative repetitive nerve stimulation (RNS) results, 73% had an abnormal RoVEMP test. The magnitude of decrement was correlated with the time since the last intake of pyridostigmine (B = 5.40; $p = 0.019$).

Conclusions
The RoVEMP test is a new neurophysiologic test that, in contrast to RNS and single-fiber EMG, is able to measure neuromuscular transmission of extraocular muscles, which are the most affected muscles in MG. Especially in diagnostically challenging patients with negative antibody tests, negative RNS results, and isolated ocular muscle weakness, the RoVEMP test has a clear added value in supporting the diagnosis of MG.

Classification of evidence
This study provides Class III evidence that RoVEMP distinguishes MG from other neuromuscular diseases.

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Glossary

AChR = acetylcholine receptor; **AUC** = area under the curve; **CI** = confidence interval; **CMS** = congenital myasthenic syndrome; **EOM** = extraocular muscle; **GMG** = generalized MG; **GO** = Graves ophthalmopathy; **LEMS** = Lambert-Eaton myasthenic syndrome; **MG** = myasthenia gravis; **MuSK** = muscle-specific kinase; **OMG** = ocular MG; **oVEMP** = ocular vestibular evoked myogenic potentials; **RNS** = repetitive nerve stimulation; **ROC** = receiver operating characteristics; **RoVEMP** = repetitive oVEMP; **SFEMG** = single-fiber EMG; **SNMG** = seronegative MG.

Myasthenia gravis (MG) is an autoimmune disease characterized by fatigable muscle weakness. Ocular muscles are involved at the onset of the disease in ≈85% of patients, causing diplopia and ptosis.[1,2] Early recognition and treatment are of great importance for patients' quality of life.[3]

Current neurophysiologic tests have a major limitation: the most commonly affected muscles, the extraocular muscles (EOMs), cannot be measured. Moreover, repetitive nerve stimulation (RNS) has a low sensitivity (0.29) in the patient subgroup in whom the diagnosis is most challenging: patients with ocular MG (OMG).[4] Single-fiber EMG (SFEMG) has a higher sensitivity in OMG (62%–97%)[4]; however, it requires a skilled neurophysiologist and is time-consuming and operator-dependent.[5]

Measurement of fatigability in the EOMs by using ocular vestibular evoked myogenic potentials (oVEMP) might be a solution to this diagnostic problem (figure 1).[6–10] Valko et al.[6] observed a decrement in the n2-p2 amplitude by applying a train of 10 repetitive oVEMP in patients with MG, analogous to the decrement observed in RNS. We refer to this technique as the repetitive oVEMP (RoVEMP) test.

We aim to validate and further investigate the diagnostic yield of RoVEMP compared with a control group of patients with a neuromuscular disease other than MG (neuromuscular controls) and a group of healthy controls. We also analyzed the effect of pyridostigmine use on RoVEMP results. Furthermore, we included a large cohort of patients with MG to analyze the sensitivity and specificity of the RoVEMP in diagnostically challenging subgroups (patients with OMG and SNMG).

Methods

Primary research question

Does RoVEMP distinguish MG from other neuromuscular diseases in a prospective case-control study (Class III evidence)?

Participants

We included a convenience cohort of patients with MG who visited the outpatient clinic of Leiden University Medical Center between 2018 and 2019 (figure 2). The minimum sample sizes for the groups were predetermined from power calculations with an expected area under the curve (AUC) of 0.8. In addition, we included patients with Lambert-Eaton myasthenic syndrome (LEMS) and genetically confirmed congenital myasthenic syndrome (CMS). We also included a group of healthy controls and a group of patients with a neuromuscular disease other than MG (neuromuscular controls). We considered the following diseases: inclusion-body myositis, facioscapulohumeral muscular dystrophy, myotonic dystrophy, myopathy, oculopharyngeal muscular dystrophy, chronic inflammatory demyelinating polyneuropathy, cranial nerve palsies (III, IV, VI), mechanical diplopia, and Graves ophthalmopathy (GO). Patients with GO were included from the Ophthalmology Department of the Leiden University Medical Center. Patients with GO form an important control group because the ocular symptoms in these patients may resemble those of patients with OMG and may cause diagnostic confusion and delay.[11–16] Patients with MG who were being treated with pyridostigmine were not asked to refrain from taking pyridostigmine before the RoVEMP test. All participants were examined for the presence of diplopia before RoVEMP testing. We recorded the time between the RoVEMP test and the last intake of pyridostigmine. We retrieved all relevant clinical information or RNS results of patients with MG and neuromuscular controls from their patient records.

The diagnosis of MG was based on a combination of clinically confirmed fluctuating muscle weakness and the presence of serum autoantibodies to the acetylcholine receptor (AChR) or muscle-specific kinase (MuSK). Seronegative MG (SNMG) was defined as fatigable muscle weakness in combination with abnormal decrement (at least 10%) during RNS, increased jitter in SFEMG testing, or a positive response to an acetylcholinesterase inhibitor.[17]

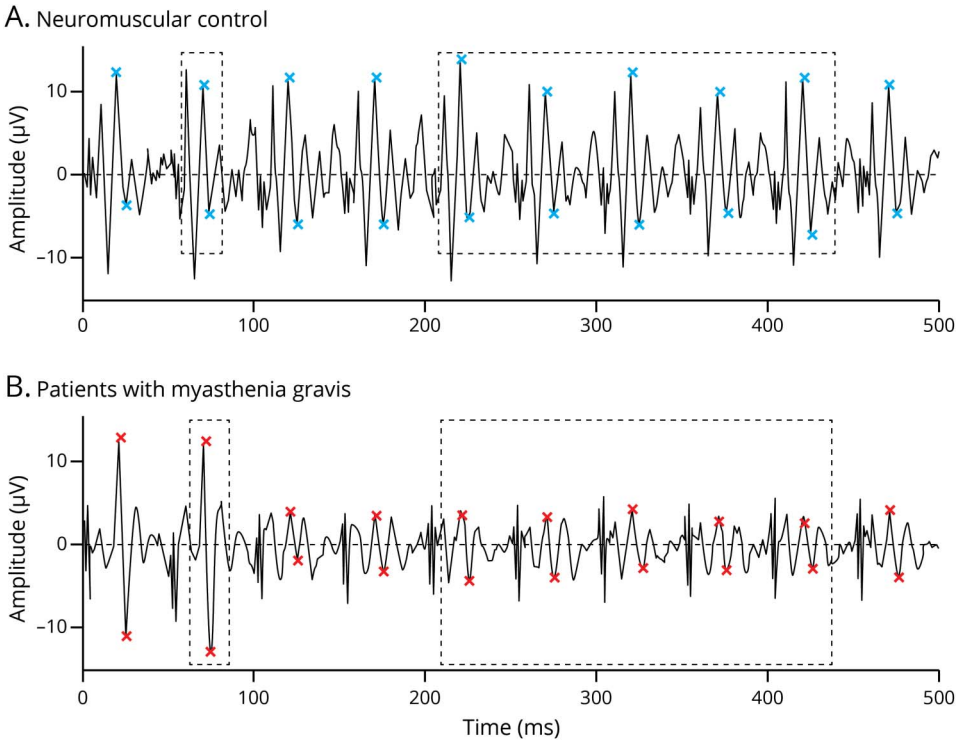
Standard protocol approvals, registrations, and patient consents

The Medical Ethics Review Committee of the Leiden University Medical Center approved the study and its use of human participants. All patients provided written informed consent before study participation.

RoVEMP test

In collaboration with the group of Valko et al.,[6] we reproduced the measurement setup to perform the RoVEMP test. The oVEMP is a multiphasic wave with the first peak at a latency of 10 milliseconds after stimulation. The placement of the surface electrodes was the same as described by Valko et al., with 2 surface electrodes directly under each eye to record myogenic activity from the inferior oblique muscles and a ground

Figure 1 RoVEMP recordings



Repetitive ocular vestibular evoked myogenic potentials (RoVEMP) test results of (A) a neuromuscular control (Graves ophthalmopathy) and (B) a patient with myasthenia gravis (MG) are shown. The oVEMP response is a multiphasic wave. For the RoVEMP test, the amplitude between the second peak (n2) and the second trough (p2) of the oVEMP response is used (n2 and p2 are indicated by colored asterisks). Decrement is calculated by comparing the n2-p2 amplitude after the second stimulation with the mean of the fifth to ninth amplitudes.

electrode on the forehead. We used a stimulation frequency of 20 Hz and applied vibrations in trains of 10 stimuli with a handheld mini-shaker (type 4810, Bruël & Kjaer, Nærum, Denmark) to the skull. We repeated these trains 40 times to improve the signal-to-noise ratio. The signals were sampled with a rate of 2,000 per second and saved with Nim Eclipse software and a Nim Eclipse recording device (Medtronic Xomed, Inc, Jacksonville, FL). The RoVEMP tests were performed by 2 physicians (R.H.P.d.M. and K.R.K.).

Signal analysis

The recorded signals were analyzed for outliers with the use of a median absolute deviation algorithm. The median absolute deviation of the signal between the stimulus artifacts is a measure for baseline fluctuations and other high-voltage artifacts, which are most commonly caused by eye-blinking during the measurement. Measurements with a median absolute deviation higher or lower than 2 SDs from the mean were considered outliers and were excluded. The remaining recorded signals were averaged. The average was high-pass filtered at 20 Hz with a Butterworth filter to correct for additional baseline fluctuations.

Decrement calculation

After all measurements were averaged, the peaks and troughs of the oVEMP signal were analyzed, and the amplitude of the oVEMP response was calculated with an Matlab script developed in house (MATLAB 2016a, The MathWorks, Natick, MA). Per measurement, all peaks and troughs were automatically analyzed (thresholding with a minimal peak prominence of 0.8 μV), and the correct peaks and troughs were automatically selected using participant-specific latency values based on visual inspection of the averaged signals. The amplitudes from all second negative peaks (n2) to the second positive peaks (p2) were calculated. The n2-p2 amplitude was used to calculate decrement because this reference (instead of N1P1, for example) was shown to result in the highest diagnostic yield. As a measure of neuromuscular transmission, the RoVEMP decrement was calculated for each eye as described previously by Valko et al.[6] with the following formula:

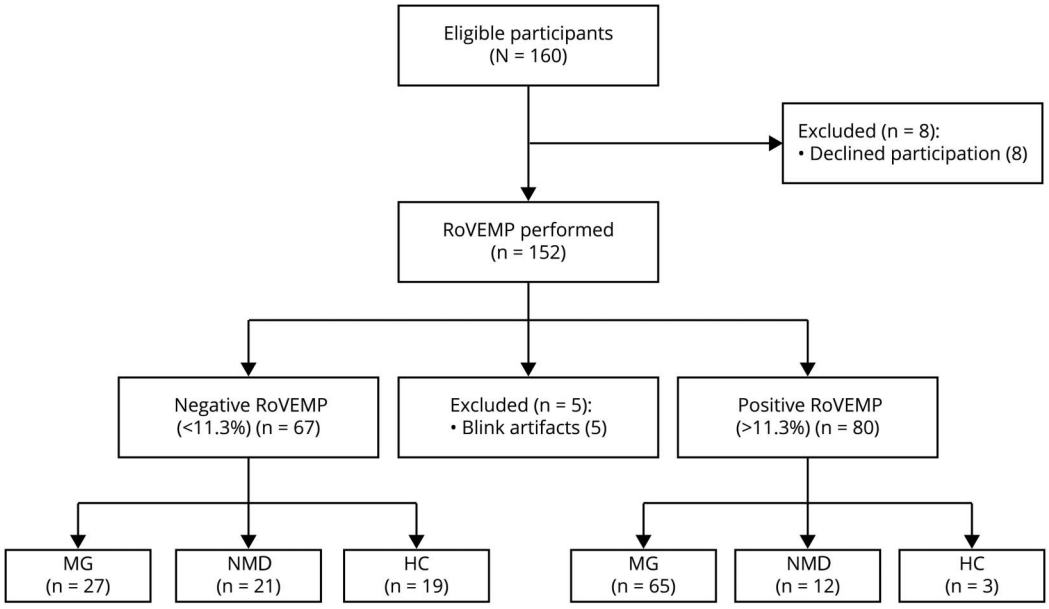
$$\text{Decrement} = 100\% - \frac{\text{Average of n2-p2 Amplitude}_{\text{5th-9th}}}{\text{n2-p2 Amplitude}_{\text{2nd}}} \times 100\%$$

Of the 2 decrements found in the 2 eyes of the participant, the highest was considered the RoVEMP decrement in that participant. An additional analysis was performed using the lowest decrement for each participant.

Statistical analysis

For comparison of decrement and other numerical variables between groups, we used an unpaired t test. To compare categorical variables between groups, we used a χ^2 test. To determine optimal oVEMP cutoff values, we created receiver operating characteristics (ROC) curves. Data are presented as number of patients (percent) for categorical variables and as mean ± SD for continuous variables. Values of $p < 0.05$ were considered significant. Statistical analyses were performed with SPSS version 23 (IBM Corp, Armonk, NY).

Figure 2 STARD flow diagram: Included participants with RoVEMP results and diagnosis



Standards for the Reporting of Diagnostic Accuracy (STARD) flow diagram showing the included participants and results for the repetitive ocular vestibular evoked myogenic potentials (RoVEMP) test at the lowest determined cutoff point. Corresponding study group is included in the bottom for myasthenia gravis (MG), neuromuscular disease controls (NMD), and healthy controls (HC).

Data availability

Anonymized data and the study protocol presented in this article will be made available at the request of a qualified investigator. Requests should be made to Dr. Tannemaat (m.r.tannemaat@lumc.nl).

Results

Participant characteristics

We included 92 patients with MG, 22 healthy controls, 33 neuromuscular controls, 4 patients with LEMS, and 2 patients with CMS. Two patients with MG had a follow-up visit at which the RoVEMP test was performed for a second time. The mean age and percentage of men were comparable among patients with MG (57 ± 18 years; 48%), healthy controls (51 ± 14 years; 46%), and neuromuscular controls (58 ± 12 years; 46%). Diplopia on examination before RoVEMP testing was found in 58% of patients with MG and 67% of neuromuscular controls. Thirty-five patients with MG had used pyridostigmine ≤4.5 hours before the RoVEMP test. The RoVEMP results of 1 patient with MG, 2 healthy controls, and 2 neuromuscular controls were not analyzable due to excessive blink artifacts and were excluded. In 1 neuromuscular control (myotonic dystrophy), increment was truncated at 100%. None of the participants reported major discomfort due to the RoVEMP test, and all patients who had experienced RNS or SFEMG before reported that the RoVEMP test was less unpleasant. Demographic and clinical baseline characteristics of all patients with MG subdivided by antibody status are shown in the table.

oVEMP decrement in MG and other groups

Mean decrement was significantly higher in patients with MG (28.4 ± 32.2%) than in healthy controls (3.2 ± 13.9%; $p < 0.001$) and neuromuscular controls (3.8 ± 26.9%; $p < 0.001$) (figure 3A). Mean decrement in patients with LEMS (41.8 ± 40.4%) and patients with CMS (29.1 ± 16.2%) was elevated, but because of the low numbers in these groups, statistical comparisons were not feasible. The results in neuromuscular controls for each disease separately are shown in figure 4. Using ROC analysis, we identified optimal decrement cutoffs for distinguishing between patients with MG and healthy controls (≥11.3%; sensitivity 71% [95% confidence interval (CI) 61–79], specificity 86% [95% CI 67–95], AUC 0.78 [95% CI 0.69–0.86]) and between patients with MG and neuromuscular controls (≥14.3%; sensitivity 67% [95% CI 57–76], specificity 82% [95% CI 66–91], AUC 0.74 [95% CI 0.65–0.83]) (figure 5, A and B). The positive and negative predictive values are 96% (95% CI 88–98) in the former ROC analysis and 41% (95% CI 33–50) in the latter. The positive and negative predictive values in the latter ROC analysis are 91% (95% CI 83–96) and 47% (95% CI 39–56), respectively. When a cutoff value of 11.3% is applied to the measurement with the lowest decrement in each participant, specificity increases to 91%, but sensitivity is reduced to 54% when healthy controls are compared to patients with MG, as described previously.[6]

RoVEMP decrement in MG subgroups

Mean decrement was comparable in patients with AChR (27.5 ± 33.0%), MuSK (29.7 ± 42.2%), and SNMG (32.6 ±

Table Comparison of demographic, clinical, and diagnostic characteristics among patients with AChR MG, MuSK MG, and SNMG

	AChR MG (n = 71)	MuSK MG (n = 7)	SNMG (n = 14)	*p* Value
Age, y	57.1 ± 18.3	54.0 ± 20.3	57.1 ± 14.4	0.908
Age at onset, y	46.3 ± 18.7	46.4 ± 17.6	46.0 ± 15.1	0.998
Sex, n (%)				
Male	36 (51)	4 (57)	4 (29)	0.278
Female	35 (49)	3 (43)	10 (71)	
Phenotype, n (%)				
Ocular	18 (25)	0 (0)	7 (50)	0.040
Generalized	53 (75)	7 (100)	7 (50)	
Thymectomy, n (%)				
Yes, with thymoma	7 (10)	0 (0)	0 (0)	0.138
Yes, without thymoma	21 (30)	1 (14)	1 (7)	
No	43 (60)	6 (86)	13 (93)	
Medication use, n (%)				
Pyridostigmine	49 (69)	1 (14)	10 (71)	0.013
Prednisone	38 (54)	5 (71)	7 (50)	0.622
Other immunosuppressants	33 (47)	4 (57)	5 (36)	0.622
RNS, n (%)				
Abnormal decrement	24/49 (49)	2/6 (33)	1/11 (9)	0.048
RoVEMP, n (%)				
Decrement	27.5 ± 33.0	29.7 ± 42.2	32.6 ± 23.2	0.861
Decrement ≥11.3%	50 (70)	5 (71)	10 (71)	0.996
Decrement ≥14.3%	47 (66)	5 (71)	10 (71)	0.904

Abbreviations: AChR = acetylcholine receptor; MG = myasthenia gravis; MuSK = muscle-specific kinase; RNS = repetitive nerve stimulation; RoVEMP = repetitive ocular vestibular evoked myogenic potentials; SNMG = seronegative MG.
Baseline characteristics of 92 patients with MG included in this study. Data are presented as number of patients (percent) for categorical variables and as mean ± SD for continuous variables.

23.2%). The mean decrement in patients with OMG (32.1 ± 23.7%) and generalized MG (GMG) (27.1 ± 34.9%) was also comparable (figure 3B). With a cutoff of ≥11.3%, a nonsignificant trend toward a higher occurrence of an abnormal RoVEMP test was found in patients with OMG (84%) compared to patients with GMG (66%; $p = 0.086$). With a cutoff of ≥14.3%, a similar difference was found (80% vs 63%; $p = 0.115$). The RoVEMP was abnormal in similar frequencies in patients with AChR, MuSK, or SNMG (table). In 6 of 7 patients with SNMG with isolated ocular weakness, the RoVEMP test was clearly abnormal, with decrements >22%.

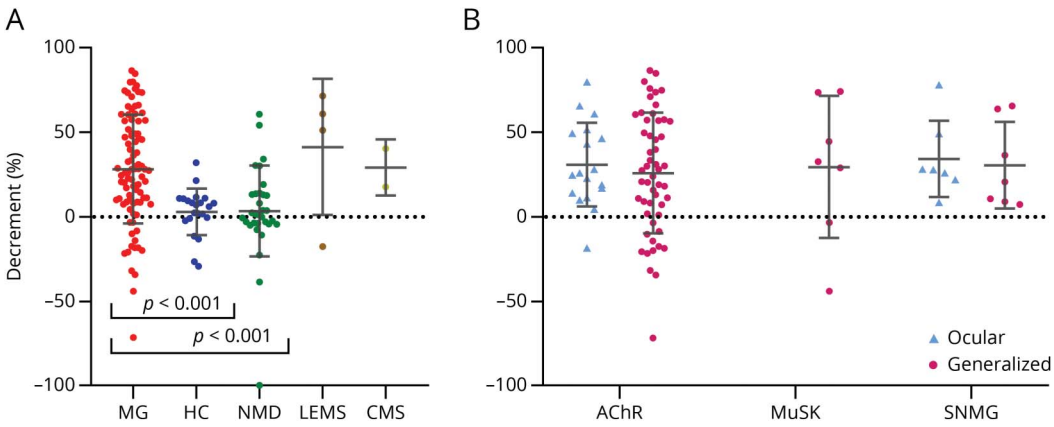
Comparison of RoVEMP and RNS

Abnormal RNS findings (decrement ≥10%) occurred significantly more often in patients with seropositive MG (47%) than in patients with SNMG (9%; $p = 0.019$) and more often in patients with GMG (51%) than in patients with OMG (16%; $p = 0.008$). The percentage of patients with an abnormal RoVEMP test and a negative RNS was significantly higher in patients with SNMG (73%) compared to patients with seropositive (AChR or MuSK) MG (40%; $p = 0.047$). These results were identical with cutoff values ≥11.3% and ≥14.3%.

Pyridostigmine effect on RoVEMP decrement

Mean decrement was significantly higher in patients with MG who did not use pyridostigmine before the RoVEMP test (33.2 ± 35.4%) compared to patients with MG who did use pyridostigmine ≤4.5 hours before the RoVEMP test (19.8 ± 23.7%; $p = 0.033$) (figure 6A). However, the percentage of patients with a RoVEMP decrement ≥11.3% was similar in both groups (73% and 67%, respectively; $p = 0.530$). With a cutoff value of ≥14.3%, a nonsignificant trend

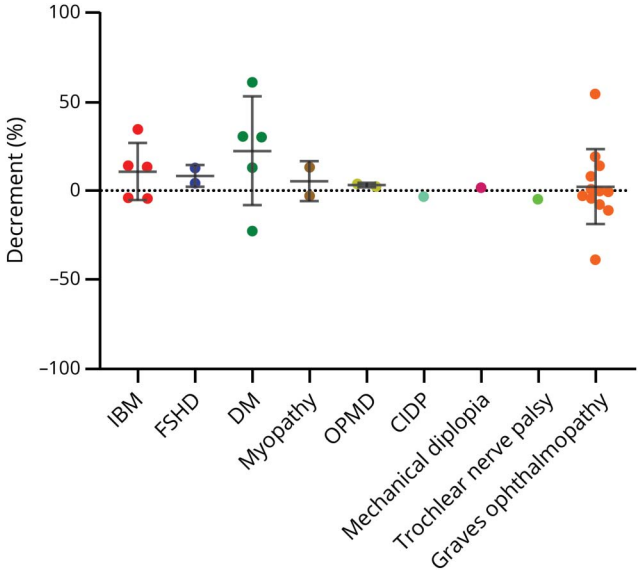
Figure 3 Individual and mean RoVEMP decrements in patients with MG, HCs, and NMDs



(A) Scatter dot plots showing repetitive ocular vestibular evoked myogenic potentials (RoVEMP) decrements in the 5 groups who participated in this study. Mean and 95% confidence interval (CI) are shown by lines and error bars. (B) Scatter dot plots showing RoVEMP decrements in patients with acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and seronegative myasthenia gravis (SNMG), subdivided by ocular and generalized phenotype. Mean and 95% CI are shown by lines and error bars. HC = healthy control; LEMS = Lambert-Eaton myasthenic syndrome; MG = myasthenia gravis; NMD = neuromuscular disease control.

toward a higher occurrence of an abnormal RoVEMP test was found in the former (73%) compared to the latter group (58%; $p = 0.133$). The magnitude of decrement was correlated with the time since the last intake of pyridostigmine (B = 5.40; $p = 0.019$) (figure 6B). In the 2 patients with a follow-up visit, RoVEMP decrements were lower on the day in which pyridostigmine was taken an hour before the test (29% and 24%) than on the day in which the patients did not take pyridostigmine before the test (66% and 45%).

Figure 4 Individual and mean RoVEMP decrements in neuromuscular disease controls subdivided by neuromuscular disease



Scatter dot plots showing repetitive ocular vestibular evoked myogenic potentials (RoVEMP) decrements in all the disease groups who together constituted the neuromuscular control group. Mean and 95% confidence interval are shown by lines and error bars. CIDP = chronic inflammatory demyelinating polyneuropathy; DM = myotonic dystrophy; FSHD = facioscapulohumeral muscular dystrophy; IBM = inclusionbodymyositis; OPMD = oculopharyngeal muscular dystrophy.

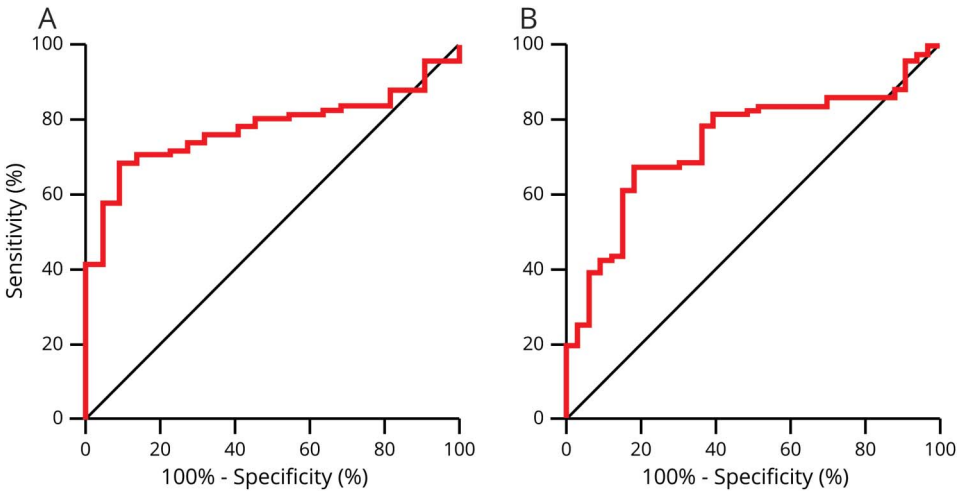
Discussion

In this study, we showed that the RoVEMP test accurately differentiates between patients with MG and patients with other neuromuscular diseases as well as healthy controls. The RoVEMP test had a high sensitivity in the diagnostically most challenging myasthenia subgroup: patients with ocular SNMG. Six of 7 of these patients had a positive RoVEMP test.

Valko et al.[6] reported an optimal decrement cutoff of ≥15.2% in a cohort of 13 patients with ocular and 14 patients with GMG compared to a healthy control group (n = 28) and found a sensitivity of 89% and a specificity of 64%. The overall sensitivity of the RoVEMP test compared to healthy controls found in our study was somewhat lower (71%). This is probably due to the fact that our cohort contained a lower percentage of patients with OMG (27% [25 pf 92]) than the cohort of Valko et al. (48% [13 of 27]). This is supported by the higher sensitivity found in patients with OMG in our cohort (84%).

As described previously, RNS is often negative in patients with SNMG or OMG.[4] In our study, RNS was abnormal in only 9% of patients with SNMG and in 16% of patients with OMG. Compared to previous studies, the sensitivity of the RNS was lower in our cohort (in both OMG and GMG). We hypothesize that this may have been caused by the fact that our patients were not newly diagnosed, and treatment for a longer period of time may have lowered the sensitivity of

Figure 5 ROC curve analyses to determine optimal cutoff values



(A) Receiver operating characteristics (ROC) curve analysis with healthy controls as reference. Optimal cutoff value >11.3%, sensitivity 71%, specificity 86%, and area under the curve (AUC) 0.78. (B) ROC curve analysis with neuromuscular controls as reference. Optimal cutoff value >14.3%, sensitivity 67%, specificity 82%, and AUC 0.74.

RNS. This hypothesis also entails the possibility that the RoVEMP test may have a higher sensitivity in a cohort of treatment-naive patients.

In SNMG, the RoVEMP test was abnormal in 73% of patients who had a normal RNS. In patients with seropositive MG, the RoVEMP test also appeared to be more sensitive than RNS (40% of patients with a negative RNS had an abnormal RoVEMP); however, this additional diagnostic value was significantly lower than in SNMG. This difference is probably due to the higher number of patients with OMG in the SNMG group. This study shows that the RoVEMP test is the only diagnostic test for MG that does not have a lower sensitivity in SNMG or OMG. On the contrary, the sensitivity of the RoVEMP test in patients with ocular SNMG, usually the most difficult subgroup to diagnose, was relatively high.

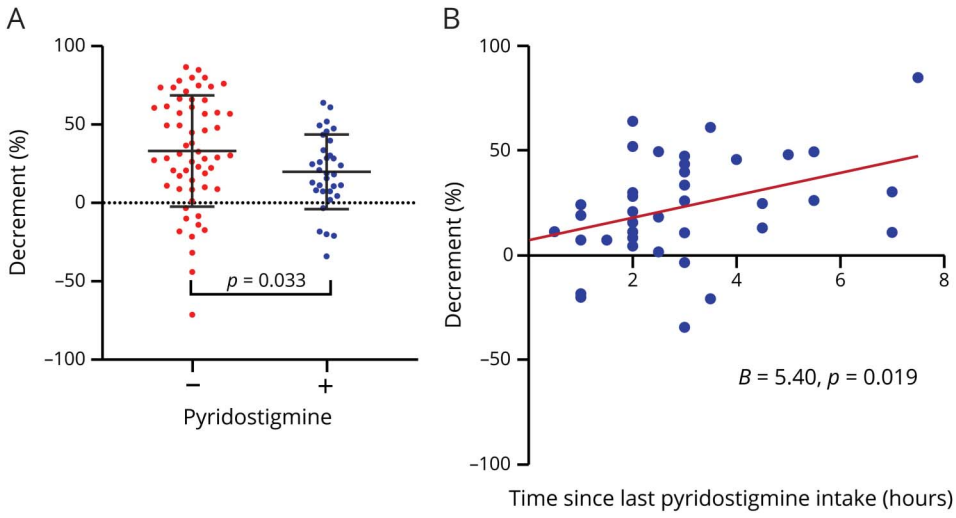
In this study, we included a low number of patients with MuSK MG (n = 7) who had a similar percentage of positive RoVEMP tests (71%) compared to patients with AChR MG. RNS has been reported to be less sensitive in MuSK MG.[5] Although the numbers are too low to draw conclusions, we suspect that the relatively high sensitivity of the RoVEMP test in MuSK MG may be due to the frequent presence of some degree of ocular weakness in this subgroup, whereas limb weakness is often absent. In fact, all of our 7 patients with MuSK MG had diplopia at the time of RoVEMP testing. Because RNS is also used in patients with LEMS and CMS, we included a small number of these patients to explore the potential value of the RoVEMP test in LEMS and CMS. Three of 4 patients with LEMS and 2 of 2 patients with CMS had an abnormal RoVEMP test in our study. Although promising, these results should be confirmed in larger cohorts.

We used an ROC analysis to identify optimal cutoff values to distinguish between patients with MG and healthy controls and between patients with MG and neuromuscular controls. The sensitivity, specificity, and AUC were similar in the 2 ROC analyses. The optimal cutoff values also were similar. Because neuromuscular controls form a better reference than healthy controls, we propose using the more conservative cutoff value found in the ROC analysis with neuromuscular controls (≥14.3%), with an overall sensitivity of 67% and specificity 82%. The calculated positive predictive value of 91% and negative predictive value of 41% show that the RoVEMP is more valuable for ruling in patients with MG than in ruling them out. Although this cutoff value lies 3.0% above that of the ROC analysis with healthy controls, the sensitivity in patients with SNMG or OMG is not affected. This cutoff value also lies closer to that proposed by Valko et al.[6] (≥15.2%).

Pyridostigmine use ≤4.5 hours before the RoVEMP test was associated with a lower magnitude of RoVEMP decrement. However, the sensitivity was not significantly different between patients who did and those who did not use pyridostigmine before the test. Still, we would recommend asking patients not to use pyridostigmine ≤4.5 hours before the RoVEMP test. We also found a significant correlation between the magnitude of decrement and the time since the last intake of pyridostigmine and observed considerably lesser decrements in 2 patients when taking pyridostigmine compared to not taking pyridostigmine. These findings support that RoVEMP decrement reflects reversible neuromuscular transmission failure, probably analogous to RNS decrement. In addition, we showed that RoVEMP decrement is not a measure for diplopia in general; the prevalence of diplopia was similar in our patients with MG and neuromuscular controls.

We found an abnormal RoVEMP test in 2 healthy controls and 6 neuromuscular controls. Some of these controls showed

Figure 6 Correlation between decrement and pyridostigmine intake



(A) Scatter dot plots showing repetitive ocular vestibular evoked myogenic potentials (RoVEMP) decrements in patients with myasthenia gravis (MG) who did not use pyridostigmine (pyridostigmine−) and patients with MG who did use pyridostigmine ≤4.5 hours before the RoVEMP test (pyridostigmine+). Mean and 95% confidence interval are shown by lines and error bars. (B) Analysis of the relation between decrement and time since last pyridostigmine intake in 39 patients with MG. The correlation between these 2 variables is shown by the linear regression line (red).

a relatively high variation in the latency of the detected peaks and a low signal-to-noise ratio. In this study, we decided to exclude RoVEMP results only when evident blink artifacts disrupted the RoVEMP signal (overall exclusion rate 3%). In further research, we will focus on quantifying the signal-to-noise ratio and establishing a method to objectively determine the confidence bounds of a single RoVEMP measurement to increase the diagnostic yield.

Limitations of this study include the single center of inclusion and our study population within a tertiary referral center that may not fully reflect the total MG population due to a referral bias. Our control group of neuromuscular patients did not reflect the whole range of patients with diplopia due to a neuromuscular disease other than MG. However, we included control patients with disorders that were previously reported to cause diagnostic confusion and delay due to similarities in presenting symptoms compared to OMG.[18] Methodologic limitations of our study are the fact that interrater reliability was not formally assessed and the fact that investigators were not blinded to clinical status. These methodologic limitations are likely to have a minimal impact because the role of the investigator is limited to placing electrodes, encouraging the patient to relax, and placing the mini-shaker, but further studies on reliability will still be needed to prove this. All postprocessing and decrement calculation were fully automated by a Matlab script. Another limitation is the (current) impossibility of including patients with excessive blinking in response to the vibrations. In this study, we have excluded 3% of the participants due to this problem. By further optimizing stimulus parameters, altering the procedure of testing in patients with excessive blinking (e.g., lowering the stimulus intensity), and optimizing postprocessing, we hope to increase diagnostic yield in future studies.[19]

The RoVEMP results of 1 patient with MG, 2 healthy controls, and 2 neuromuscular controls were not analyzable due to excessive blink artifacts and were excluded.

The RoVEMP test is a new neurophysiologic test that, in contrast to RNS and SFEMG, is able to measure neuromuscular transmission of EOMs, which are the most affected muscles in MG. Because the test is quick (10–15 minutes), less invasive than RNS and SFEMG, and easy to perform, we recommend including the RoVEMP test in the routine diagnostic evaluation of patients with suspected MG. Especially in diagnostically challenging patients with negative antibody tests, negative RNS results, and isolated ocular muscle weakness, the RoVEMP test has a clear added value in supporting the diagnosis of MG.

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Kevin R. Keene, MD	Leiden University Medical Center, the Netherlands	Conception and design of the study; acquisition and analysis of data; statistical analysis; drafting a significant portion of the manuscript or figures
Magdalena A. Wirth, MD	University Hospital Zurich, University of Zurich, Switzerland	Conception and design of the study
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Umesh A. Badrising, MD, PhD	Leiden University Medical Center, the Netherlands	Acquisition and analysis of data
Jan J. Verschuuren, MD, PhD	Leiden University Medical Center, the Netherlands	Conception and design of the study; drafting a significant portion of the manuscript or figures
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