Is the Stimulation Frequency of the Repetitive Nerve Stimulation Test that You Choose Appropriate?

Yuan-Ting Sun and Thy-Sheng Lin

Abstract- The repetitive nerve stimulation test (RNST) has been a useful method in the diagnosis of myasthenia gravis (MG). In clinical practice, a short train of repetitive stimulation is usually given at 3 Hz. Although it was documented that lower stimulation frequencies could offer a greater sensitivity, no study has been done to testify the most sensitive stimulation frequency for RNST. To find out an optimal stimulation frequency, we performed RNST at 0.5, 1, 3, 5, 7, 10, 15 and 20 Hz in 15 MG patients and 5 healthy subjects. The results showed that the decremental response was most often seen at 7 Hz rather than at 3 Hz. To augment the sensitivity in the diagnosis of MG, RNST should be performed stimulation not only at 3Hz but also at other frequencies, preferably 7 Hz.

Key Words: Myasthenia gravis, Repetitive nerve stimulation test

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INTRODUCTION

The repetitive nerve stimulation test (RNST) has been a useful method in evaluating the neuromuscular transmission. The diagnosis of myasthenia gravis (MG) can be supported by obtaining a decremental response in RNST with a train of stimulation at low frequency[1]. Previous studies showed that the sensitivity of RNST was influenced by various parameters, such as temperature[2], severity of clinical condition[3-5], different nerves for stimulation, different muscles for recording[6-9], and titer of anti-acetylcholine receptor antibody[3]. The decremental response was demonstrated more frequently at low stimulation frequencies than higher ones. According to the guidelines of American Association of Electrodiagnostic Medicine declared in 2001[1], RNST should be performed at the stimulation frequency between 2 and 5 Hz. However, there was no specific study designed to clarify the optimal stimulation frequency for RNST, which yielded the best sensitivity in the diagnosis of MG. This study was aimed to find the optimal stimulation frequency of RNST.

SUBJECTS AND METHODS

Patients with generalized MG regularly followed up

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at our out- patient unit for at least 6 months were enrolled. The diagnosis of MG was based on clinical symptoms and signs, a positive result of edrophonium pharmacological test and proven thymic lesions on chest computed tomography. The oral medications, either pyridostigmine or prednisolone, were used continuously during this study. To verify the RNST technique, we also enrolled five normal healthy persons as the control group.

Every subject received the same procedures of RNST. They were in supine position as relaxed as possible. The procedures were performed in a room kept at a constant room-temperature of 25 ˚C. Nobody was in fever and their skin temperature measured on forearm was kept between 32 and 33 ˚C. We selected the right abductor pollicis brevis (APB) and right facial muscles for study. The proximal limb muscles were not selected because of technical difficulty and painful sensation in high frequency stimulation. RNST was done on a Viking IV EMG machine (Nicolet, USA). Ten repetitive stimuli at supra-maximal intensity were applied on median or facial nerves. The stimulation frequency was set at 0.5, 1, 3, 5, 7, 10, 15, and 20 Hz, respectively. A pause interval was given between each acquisition to offer an adequate recovery from neuromuscular transmission depression.

The amplitudes of compound motor action potential (CMAP) were recorded. For a respective train, a decremental response was defined as: 1. progressively decremented amplitude on the first few consecutive CMAPs and 2. at least 10% decline of the amplitude of minimal CMAP compared to that of the first one.

RESULTS

Control healthy subjects included 2 males and 3 females, age ranged 29-43 years (mean = 32). Despite the stimulation frequency, no decremental response was seen in these persons. Three of them showed visualized pseudofacilitation at frequency higher than 15 Hz.

Fifteen generalized MG patients were enrolled. They were 6 males and 9 females, and the ages ranged 17-55 years (mean = 43.8). Their demographic data are listed in Table. Seven (46.7%) of them showed decrements on APB and 11 (73.3%) showed decrements on facial muscles (Fig. 1). Two had decrements on APB, but a normal facial muscle response. Six had decrements on facial muscles but a normal APB response. Decremental responses in either one or both muscles were seen in 13 patients (86.7%). Two patients had no abnormal decrement on either muscle. RNST was more sensitive in facial muscles. This finding was consistent with documented results. For muscles on which the decremental responses were presented, the smallest CMAPs (the strongest decremental response) were obtained at stimulation frequencies between 5 and 20 Hz (Table), rather than at the frequency of 3 Hz.

Concerning the stimulation frequency, there was an increment in the probability of decremental response at the stimulation frequency being increased from 0.5 up to 7 Hz (Fig. 2). This phenomenon was seen on both APB and facial muscles. Beyond 7-Hz stimulation, the facial muscle showed a reciprocally decrease in the probability of decremental response while the probability did not

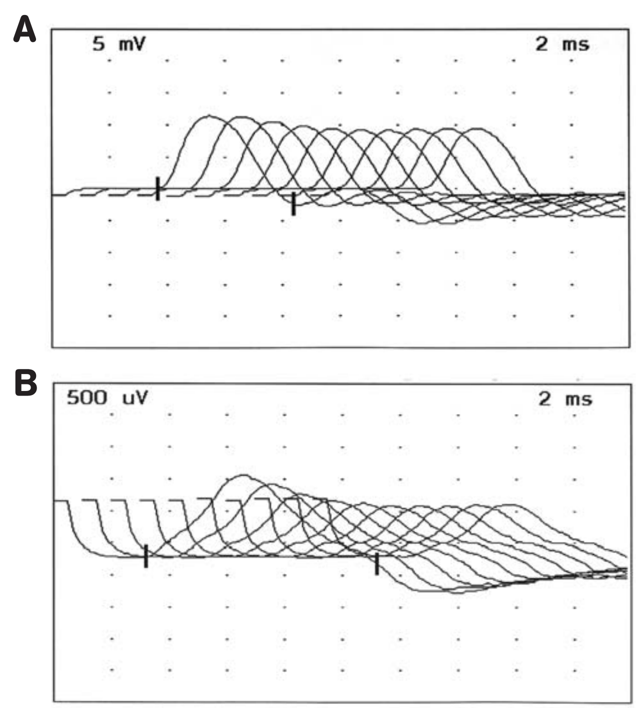

Figure 1. A sample of decremental response in (A) APB and (B) facial muscles, all at 7-Hz stimulation in Patient 4.

Table. *Clinical summaries of myasthenic patients*

Pt	Age (Gender)	Disease duration (month)	Thymic lesion	Thymectomy	Med*	Decremental response (APB/Facial)								% decrement of the smallest CMAP(Hz) #	
						.5	1	3	5	7	10	15	20	APB	Facial
1	17 (F)	8	-	-	P	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-	-
2	50 (M)	24	-	+	P,S	-/-	-/+	-/+	-/+	-/+	-/+	-/-	-/-	-	19% (10Hz)
3	41 (F)	22	-	-	P	-/-	-/-	-/-	-/+	-/+	-/-	-/-	-/-	-	27% (5Hz)
4	39 (F)	144	-	+	P,S	-/-	-/+	+/+	+/+	+/+	+/+	-/+	-/+	19% (5Hz)	39% (7Hz)
5	69 (F)	96	-	-	P,S	-/-	-/-	-/-	-/+	-/-	-/-	+/+	+/+	40% (20Hz)	25% (20Hz)
6	50 (F)	15	+	+	P,S	-/-	-/-	-/-	-/-	+/-	+/-	+/-	+/-	25% (20Hz)	-
7	55 (F)	72	+	+	P,S,A	-/-	-/-	+/-	+/-	-/-	-/-	-/-	-/-	27% (5Hz)	-
8	55 (M)	54	+	+	P,S,A	-/-	-/+	-/+	-/+	+/+	+/+	+/+	+/+	16% (10Hz)	53% (7Hz)
9	30 (F)	55	+	+	P,S	-/-	-/-	-/+	-/+	-/+	-/+	-/+	-/+	-	33% (20Hz)
10	43 (M)	84	+	+	P,S	-/-	-/-	-/-	-/+	-/+	-/+	-/-	-/-	-	18% (5Hz)
11	42 (F)	8	+	+	P,S	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-	-
12	29 (F)	161	+	+	P,S	-/-	-/-	+/-	+/-	+/+	+/+	+/-	+/-	12% (5Hz)	13% (10Hz)
13	47 (F)	6	-	-	-	-/-	-/-	-/-	-/-	-/+	-/+	-/+	-/+	-	27% (20Hz)
14	37 (F)	288	+	+	P,S,A	-/-	-/+	+/+	+/+	+/+	+/+	+/+	+/+	32% (20Hz)	47% (5Hz)
15	53 (M)	134	+	+	P,S	-/-	-/-	-/+	-/+	-/+	-/+	-/+	-/+	-	16% (5Hz)

* Medications: P -pyridostigmine; S - steroid; A - azathioprine.
# stimulation frequency at which the smallest CMAP was obtained.

change on APB. At 7-Hz stimulation, there were 73% patients presenting with decremental response on either APB or facial muscles. The decremental response was only obtained in 53% patients while the stimulation was performed at 3 Hz.

Considering the cumulated probabilities of decremental response from 0.5 to 20 Hz, a gradual increase at low frequency was shown, and the plateau was reached at high frequency (Fig. 3). One patient (No. 5) with decremental response on APB at 15-Hz stimulation did not have any decrement at frequencies lower than 15 Hz. Nevertheless, her facial muscle presented with a decremental response at 5 Hz. Consequently, the cumulated probability of decremental response on either muscle did not increase as the stimulation frequency was given beyond 7 Hz.

DISCUSSION

RNST was firstly reported by Harvey and Masland in 1941[10]. They studied three patients of typical MG by stimulating ulnar nerves and recording at the abductor

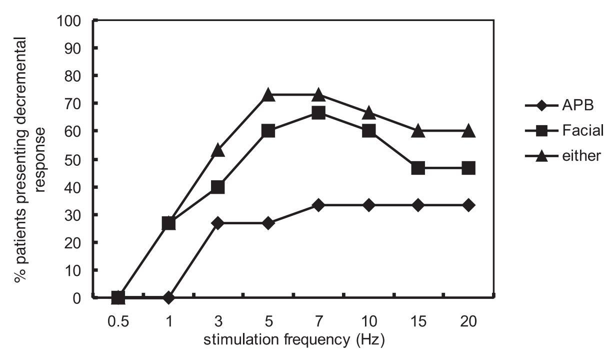

Figure 2. Probability of presenting a decremental response in patient group given different stimulation frequency.

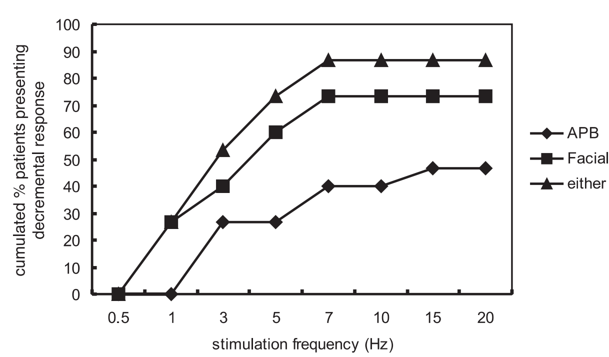

Figure 3. Cumulated probability of obtaining decremental response from stimulation frequency of 0.5 Hz to 20 Hz.

digiti quinti. The results showed that the amount of decrement was greater at 13 Hz, and relatively lesser at 43 Hz and 60 Hz. Botelho et al[11] further studied 21 MG patients with the methods of Harvey and Masland[10], giving stimulation frequencies at 3, 10 and 25 Hz. The amplitude ratio of 5th to first potential was calculated. In MG patient group, the ratio was 0.82 when the frequency of stimulation was at 3 Hz, 0.87 at 10 Hz and 0.85 at 25 Hz. Three patients showed a significant decrement at stimulation frequency of 25 Hz, but not at 3 Hz. Five had a significant decrement only at 3 Hz and not at 25 Hz, and eight had decrements both at 3 and 25 Hz stimulation. The authors suggested that RNST should be recorded at both low and high frequencies of stimulation to increase the reliability of the procedure.

In 1971, Özdemir and Young[12] studied 30 patients with MG and 30 normal subjects. Stimuli were given at the frequencies of 1, 3, 5, 8, 10, 15 and 25 Hz. The potentials were recorded from the abductor digiti minimi, flexor carpi radialis and deltoid muscles. In 82 tested muscles, 38 showed a decrement at 5 Hz of stimulation frequency; 34 at 3 Hz, 19 at 8-10 Hz, 12 at 15 Hz, 5 at 25 Hz and 1 at 1 Hz. However, there was no data describing the number of muscles that showed decrements at 8 and 10 Hz separately. The findings only suggested that 3 Hz and 5 Hz of stimulation frequency were more favored in RNST. Decrement was more frequently noted at lower rates of stimulation, particularly at 5 Hz. Mayer and Williams[13] applied RNST at the frequency of 3, 10, 30, 40 and 50 Hz on eight patients with MG also showed that the decrement was mostly observed at 3 Hz stimuli. In 2003, Niks et al.[6] studied 25 patients with MG. RNST was abnormal more often at 3 and 5 Hz than at 1 Hz for both generalized and ocular MG groups. The detailed numbers were not shown in the literature but they concluded that RNST was more often seen at 3 and 5 Hz then at 1 Hz for both groups.

Authors mentioned above had clarified that the decrement was mostly observed at low frequencies rather than at high frequencies. By reviewing these documents, one may believe that RNST should be performed at the frequencies between 3 and 5 Hz. The sensitivity seemed to be decreased when the stimulation frequencies were above 10 Hz. This inferred that the probability of a decremental response might fall between 5 to 10 Hz. In this study, however, we showed that the optimal stimulation frequency of RNST was 7 Hz (Fig. 2). Besides, the cumulated probability of decremental responses did not increase beyond 7Hz (Fig. 3), meaning that a frequency higher than 7Hz would not be necessary.

In repetitive discharges, the available transmitter in nerve terminals was reduced gradually, a phenomenon called "quanta depression"[14]. This phenomenon had a devastating effect on myasthenic junctions, on which a low quantal response existed already due to the receptor defect. Consequently, more and more neuromuscular transmission would be "blocked", resulting in a gradual decrement in the CMAP amplitude. This effect would be greater in a higher stimulation frequency than a lower one. The results of increasing probability and degree of decremental responses at frequencies from 0.5Hz to 7 Hz were in agreement with this effect.

On the contrary, a higher frequency repetitive discharge caused accumulation of calcium ion in the nerve terminals, inducing "calcium facilitation" that enhanced the available transmitter store[15,16]. This phenomenon compensated the effect of quantal depression and decreased the probability of "block", resulting in a less decrement of the CMAP amplitude. From the previous results of single fiber EMG studies[17,18] and animal studies[19], investigators suggested that the effect of calcium facilitation would become physiologically significant when the firing frequency was at or beyond 10 Hz. In our study, the dwindling decrement at the stimulation frequency higher than 10Hz further confirmed this argument.

Several documents supported that the diagnostic sensitivity of RNST was increased in more severe cases, while the severity was graded according to the classification recommended by the Medical Advisory Board of the Myasthenia Gravis Foundation[4] or by Osserman classification[3,5]. In our study, some of the patients had mild ptosis or minimal limbs weakness but all of them were stable when the RNST was performed. Therefore, the correlation between clinical severity and the sensitivity of RNST was not shown. All the MG patients did not stop medication for the study due to our ethic concern since drug withdrawal may induce a deterioration of clinical condition. Since RNST was usually applied to patients in initial visiting, the diagnostic sensitivity should not be reduced yet no matter how severe the clinical state was. It was extraordinarily appreciable when the clinical symptoms were mild, as the condition of our objectives.

In a clinical point of view, RNST is not a pretty sensitive test for the diagnosis of MG, so that clinicians should make the diagnosis according to lots of information, including clinical symptoms and signs, presence of acetylcholine receptor antibodies, positive edrophonium pharmacological test, single fiber electromyography and RNST. Nevertheless, to increase the positive detection rate of RNST is quite useful to help make the diagnosis of MG. Our results showed that the most obvious decrement in RNST was not always presented at the stimulation frequency of 3 Hz, which used to be selected in clinical EMG laboratory. Instead, the highest positive detection rate was obtained in 7-Hz stimulation. In all patients on whom the decremental response was shown at frequency beyond 7 Hz, it was already observed at frequency below 7 Hz. As we knew, increasing the stimulation frequency could elicit a more prominent decrement but it also augmented the calcium facilitation and movement artifacts that interfered the exact measurements. Therefore, even 7 Hz stimulation frequency might not provide the most obvious decrements, it offered the most ideal sensitivity in detection of decremental response. We demonstrated a practical trial to find out the most appropriate stimulation frequency in RNST. In this perspective, we suggest that RNST should be performed not only at the traditionally 3-Hz stimulation but also at other frequencies, preferably at 7 Hz.

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