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Supramaximal responses can be elicited in hand muscles by magnetic stimulation of the cervical motor roots

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Background
The amplitude of compound muscle action potentials (CMAPs) evoked in response to magnetic cervical motor root stimulation (MRS) has rarely been used as a diagnostic parameter because of the difficulty in obtaining supramaximal CMAPs.

Objective
To clarify whether supramaximal CMAPs could be elicited by MRS, and if so, whether their amplitude and area could be used to evaluate the conduction of proximal motor roots.

Method
With the use of a custom-made high-power magnetic stimulator, the CMAPs evoked in response to MRS of the first dorsal interosseous, abductor digiti minimi, and abductor pollicis brevis (APB) muscles were compared with those evoked by electrical stimulation at the wrist, brachial plexus, and cervical motor roots. The collision technique was also used to exclude volume conduction. The correlation between MRS-induced CMAP latency and body height was evaluated.

Results
In 32 of 36 normal subjects, supramaximal CMAPs were obtained in response to MRS. The size of CMAPs occurring in response to MRS was the same as the size of those occurring in response to high-voltage electrical cervical motor root stimulation. The collision technique revealed that the APB muscle was highly contaminated by volume conduction from adjacent muscles. CMAP latency correlated significantly with body height.

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Conclusions
Supramaximal CMAPs can be obtained in most normal subjects. In subjects exhibiting confirmed supramaximal CMAPs in response to MRS, not only the latency of these CMAPs but also their amplitude and area can be clinically useful, excluding CMAPs in the APB muscle.

Keywords compound muscle action potential; magnetic stimulation; motor-evoked potential; peripheral nerve

Magnetic stimulation has been widely used to evaluate central and peripheral motor conduction in humans ever since its initial clinical application.[1] Response latency has frequently been used as a parameter aiding in the diagnosis of many relevant conditions. Response amplitude, in contrast, has rarely been used for diagnostic purposes, probably because magnetic stimulation cannot always evoke supramaximal responses.[2-4]

In this study, we demonstrate that supramaximal responses can be obtained in response to magnetic cervical motor root stimulation (MRS) by using a magnetic stimulator that is more powerful than most. We compared supramaximal responses obtained in response to MRS with those obtained in response to electrical stimulation at the wrist, Erb's point (EP), and the cervical motor roots (Root). Furthermore, we studied the relationship between response latency and body height.

Subjects and methods

Subjects

The subjects enrolled in this study were 36 right-handed healthy volunteers (23 men and 13 women; age range, 24-57 years [mean ± SD, 34.2 ± 7.4 years]) without any history of cervical spondylosis, diabetes mellitus, central nervous system disorders, peripheral neuropathies, or other neuromuscular diseases. The mean ± SD of their body heights was 167.3 ± 8.0 cm (range: 153-182 cm). One patient was recruited to show the clinical use of our method, which is described in detail in the *Results* section. The results of this patient will be given as a case presentation. Written informed consent was obtained from all subjects. The experiments were performed according to the Declaration of Helsinki; and the procedures were approved by the Ethics Committee of the University of Tokyo.

Recording

During the examination, subjects were seated on a reclining chair with their arms relaxed on the arm rests. Compound muscle action potentials (CMAPs) were recorded from the following three distal muscles: the first dorsal interosseous ([FDI] C8-T1; ulnar nerve), the abductor digiti minimi ([ADM] C8-T1; ulnar nerve), and the abductor pollicis brevis ([APB] C7-T1; median nerve). Disposable silver-silver chloride disk electrodes, 9 mm in diameter, were placed in a belly-tendon montage. Signals were amplified through a Biotop amplifier (GE Marquette Medical Systems, Tokyo, Japan) with filters set at 20 Hz and 3 kHz, and recorded onto a computer (Signal Processor DP-1200; GE Marquette Medical Systems). Subjects' skin temperature was maintained at around 33°C-34°C. At least three CMAPs, either supramaximal or at the stimulus intensity of maximal stimulator output, were recorded from each subject to confirm the reproducibility of the findings. The peak-to-peak amplitude (mV), negative area (mV × milliseconds), and onset latency (milliseconds) of each CMAP were measured. The SPSS 14 statistical software package (SPSS, Chicago, IL) was used for all statistical analyses. P values less than .05 were considered significant.

Stimulation

MRS was delivered through a custom-built enhanced power Magstim 200 stimulator (Magstim, Whitland, UK) with a round coil 10 cm in mean diameter; this stimulator is about 1.4 times as powerful as the commercially available Magstim 200 stimulator. Electrical stimulation at the wrist was delivered through a conventional electrical stimulator (Electronic stimulator 3F46, NEC-San Ei, Tokyo, Japan), whereas electrical stimulation at the EP and the Root (electrical cervical motor root stimulation [ERS]) was delivered through a D180A high-voltage electrical stimulator (Digitimer, Welwyn Garden City, UK).

For MRS, the upper edge of a round coil was positioned on the seventh cervical (C7) spinous process so that a part of its edge was over the exit of each spinal nerve from the intervertebral foramina. With the coil firmly held against the spine, an examiner pulled the subject's chest backward so that the coil was as close as possible to the target spinal nerves. The coil currents were directed clockwise as seen from behind in our examination of the right hand muscles so that the induced currents in the body were directed from the muscles to the spinal cord at the upper edge of the coil (Figure 1). A previous study has confirmed that this direction is suitable for producing maximal CMAPs (minimal threshold) in MRS.[4] The stimulus intensity was gradually increased until supramaximal CMAPs were obtained.

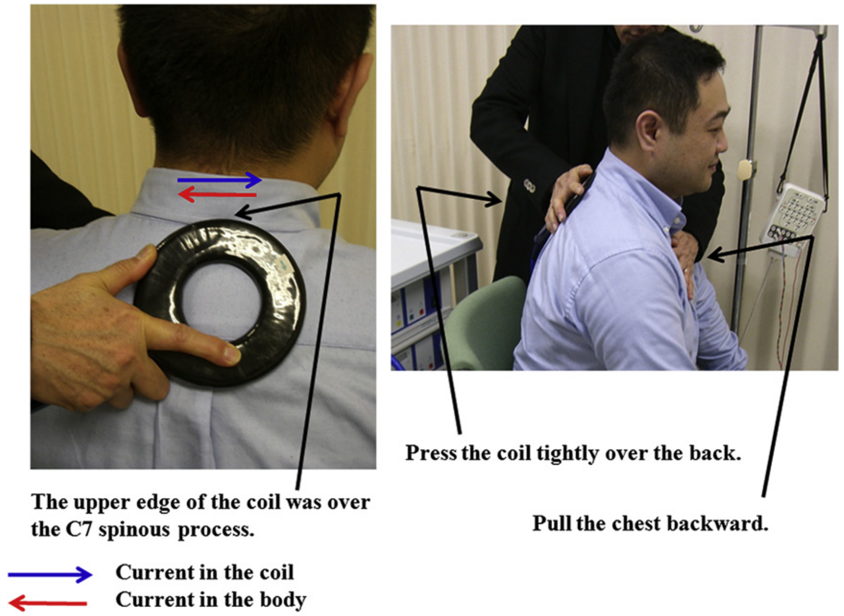

Figure 1 Back and lateral views of magnetic cervical motor root stimulation. The examiner is firmly pressing a round coil to the subject's back and forcefully pulling his chest backward.

We considered a supramaximal CMAP to have been obtained only when the size of superimposed CMAPs was saturated before the stimulus intensity reached a value equal to 1.3 times the lowest intensity that resulted in a maximal CMAP.

Electrical stimuli were applied at the wrist, EP, and Root. At the wrist and EP, each anode was placed a few centimeters proximal to the cathode. At the Root, a cathode was placed over the C7 spinous process, and an anode was placed 5 cm rostral to it.[5,6] All electrodes were then securely attached to the skin. The stimulus intensity was increased gradually until a supramaximal CMAP was obtained (i.e., until the stimulus intensity reached a value 1.3 times that of the lowest intensity capable of eliciting a maximal CMAP).

Experiment 1: Collision experiment

Nine subjects participated in this experiment. Given that MRS activates several nerves simultaneously because each root connects with several peripheral nerves, it seemed likely that volume conduction from nontarget muscles might affect the size of CMAPs occurring in response to MRS. Our collision experiment was designed to determine the degree to which this occurs.[7]

CMAPs from the right hand muscles were elicited by simultaneous MRS and electrical stimulation at the wrist and recorded. We expected that, if CMAPs were produced in response to MRS from the target muscle only, MRS would elicit no potentials because the orthodromic descending impulses generated by MRS would completely collide with the antidromic ascending impulses generated by wrist stimulation. If, on the other hand, some other nontarget muscles were contributing to the CMAPs in response to MRS (volume conduction effect), or if the recorded muscle were partly innervated by nontarget nerves, then MRS would provoke some potential at a longer latency than CMAPs not contaminated by volume conduction. The amplitude of the later potential was expressed as a percentage relative to that of the CMAPs in response to wrist stimulation. This value indicated the amount of volume conduction from other muscles that was contaminating the CMAPs. In our experiments, wrist stimulation was delivered to the ulnar (for FDI and ADM) or median nerve (for APB).

Experiment 2: Analyses of supramaximal CMAPs evoked by MRS

All 36 subjects participated in this experiment. CMAPs were recorded from the right FDI and ADM muscles in all subjects (72 muscles). APB was excluded because of considerable volume conduction (discussed in *Results, experiment 1*).

We determined how often supramaximal CMAPs could be obtained in response to MRS. If supramaximal CMAPs were obtained, the ratios of the amplitude and area of MRS-induced CMAPs and of CMAPs induced by electrical stimulation to the EP to those of wrist stimulation-induced CMAP were calculated, as were the ratios of the amplitude and area of MRS-induced CMAP to those of CMAPs induced by electrical stimulation to the EP.

To analyze the relationship between body height and CMAP latency, we performed a linear regression analysis.

Moreover, to analyze the difference between the responses generated in the two sides of each individual's body, CMAPs were also recorded from the left FDI and ADM muscles in 22 of 36 subjects (44 muscles).

Experiment 3: Comparison between MRS and ERS

Twenty-two subjects exhibiting supramaximal CMAPs participated in this experiment. CMAPs were recorded from bilateral FDI and ADM muscles. To confirm supramaximal CMAPs, we compared the amplitudes of MRS-induced CMAPs with those of ERS-induced CMAPs using the paired *t* test.

Results

Subjects reported that the discomfort caused by MRS delivered by our high-power stimulator was not different from that caused by MRS delivered by a standard stimulator; the form of MRS used in the present study was well tolerated by all subjects. No side effects were noted. Figure 2 illustrates an example of supramaximal CMAPs recorded from the FDI of one subject.

Experiment 1: Collision experiment

Representative waveforms of the collision experiment are shown in Figure 3. The amplitudes of late responses were very small in the FDI (Figure 3, left) and the ADM (data not shown), whereas responses of considerable amplitude were elicited in the APB (Figure 3, right). The amplitudes of the later responses, expressed as percentages relative to the CMAP amplitudes, were 8.2% ± 3.0% in the FDI, 3.2% ± 1.6% in the ADM, and 28.8% ± 15.0% in the APB (mean ± SD).

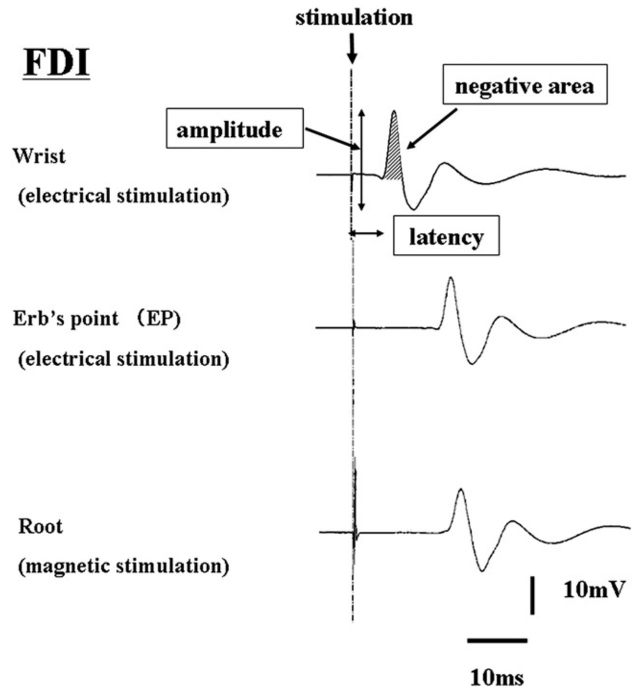

Figure 2 Representative waveforms of compound muscle action potentials (CMAPs) in one subject. CMAPs are elicited by means of electrical stimulation at the wrist and at Erb's point (EP) as well as by means of magnetic stimulation at the cervical motor roots (Root), and recorded at the first dorsal interosseous (FDI) muscle.

Experiment 2: Analyses of supramaximal CMAPs evoked in response to MRS

In 32 of 36 subjects (19 men, 13 women; age range 23-57 years [mean ± SD, 34.7 ± 7.6 years]; body height 153-179 cm [mean ± SD, 165.9 ± 7.3 cm]), MRS induced supramaximal CMAPs, that is, CMAPs did not increase in size even when the stimulus intensity was increased to

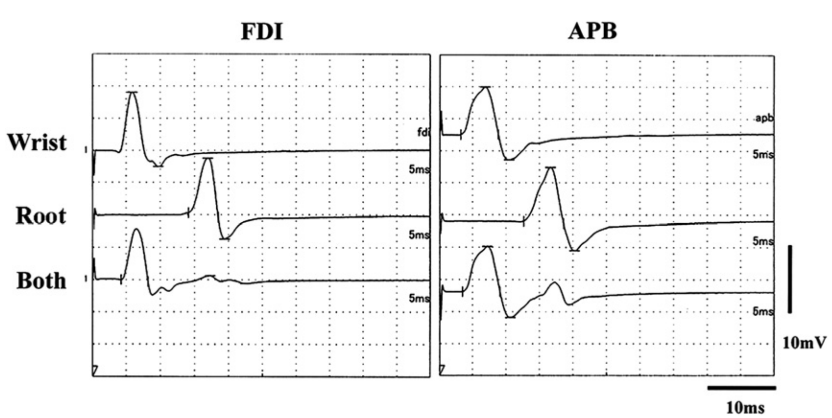

Figure 3 Responses in collision experiment. Compound muscle action potentials (CMAPs) elicited by means of electrical stimulation at the wrist, magnetic stimulation at the cervical motor roots (Root), and simultaneous stimulation at the wrist and Root are shown at the first dorsal interosseus (FDI) (left) and the abductor pollicis brevis (APB) (right). At the wrist, the ulnar nerve is stimulated to elicit responses from the FDI and the median nerve is stimulated to elicit responses from the APB. A very small late response is obtained by simultaneous stimulation in the FDI, whereas a later response of considerable size occurs in the APB.

1.3 times the minimal value that induced a maximal CMAP. This final intensity corresponded to 60-95% of the maximal stimulator output. In the four remaining subjects, supramaximal CMAPs could not be elicited even by using the maximal stimulator output; all four subjects were comparatively large and deep-chested men with heights ranging from 176-182 cm.

The amplitude, area and latency data obtained from the 32 subjects exhibiting supramaximal CMAPs are shown in Table 1. In the FDI, the CMAP amplitude ratio of Root/EP was 91.9% ± 6.7% (mean ± SD); the lowest normal limit was 78% (mean −2 SD). The area ratio of Root/EP was 96.8% ± 9.1%; the lowest normal limit was 78%. In the ADM, the CMAP amplitude ratio of Root/EP was 93.5% ± 8.6%; the lowest limit was 72%. The area ratio of Root/EP was 94.7% ± 8.0%; the lowest limit was 78%.

In the FDI, the correlation between CMAP latency after MRS and body height is shown in Figure 4. A significant and positive linear relation was observed ($P < .001$; latency = 0.11 × body height – 5.04). A similar correlation was observed in the ADM ($P < .001$; latency = 0.12 × body height – 6.74).

Experiment 3: Comparison between MRS and ERS

Among the 22 subjects who participated in this experiment, there was no significant difference in amplitude, area or latency between CMAPs occurring in response to MRS and those occurring in response to ERS in either the FDI or the ADM muscles (FDI amplitude: MRS 13.5 ± 3.1 mV, ERS 13.2 ± 3.4 mV, P = .218; area: MRS 19.7 ± 4.5 mV × millisecond, ERS 19.2 ± 4.8 mV × millisecond, P = .077; latency: MRS 12.9 ± 1.0 millisecond, ERS 12.9 ± 1.0 millisecond, P = .609; ADM amplitude: MRS 11.7 ± 2.2 mV, ERS 11.8 ± 2.5 mV, P = .830; area: MRS 19.8 ± 4.1 mV × millisecond, ERS 19.5 ± 4.4 mV × millisecond, P = .183; latency: MRS 12.6 ± 1.2 milliseconds, ERS 12.6 ± 1.2 milliseconds, P = .333).

Case presentation

Here we report on one patient whose response to MRS provided us with clinically useful information concerning the proximal regions of his peripheral nerves.

A 57-year-old man complained of acute shoulder pain and had muscular weakness of the right arm develop 3 days later. The clinical diagnosis was neuralgic amyotrophy. Conventional nerve conduction studies were all normal. F-wave latency was within the normal range, although the occurrence rate of F-waves was reduced to 50% of normal. Figure 5 shows CMAPs from the right ADM elicited in response to MRS or electrical stimulation at several sites. The CMAPs in response to electrical stimulation at the

Table 1 Data from subjects exhibiting supramaximal CMAPs

	FDI	ADM
Peak-to-peak amplitude (mV)		
Wrist	15.9 ± 4.0	15.6 ± 3.3
EP	14.6 ± 3.5	12.8 ± 2.7
Root	13.4 ± 3.2	11.9 ± 2.5
Root (laterality)	2.1 ± 1.7	2.0 ± 1.7
Ratio (%)		
EP/wrist	92.6 ± 10.6 (77-125)	82.7 ± 7.4 (64-98)
Root/wrist	85.2 ± 12.5 (60-118)	77.3 ± 10.0 (53-98)
Root/EP	91.9 ± 6.7 (78-112)	93.5 ± 8.6 (75-123)
Negative area (mV × milliseconds)		
Wrist	20.4 ± 5.2	23.5 ± 5.4
EP	20.4 ± 5.3	20.6 ± 4.4
Root	19.6 ± 4.7	19.4 ± 4.2
Root (laterality)	3.1 ± 2.2	4.3 ± 3.5
Ratio (%)		
EP/wrist	100.0 ± 7.9 (84-117)	88.4 ± 8.2 (71-113)
Root/wrist	96.9 ± 11.8 (74-125)	83.8 ± 10.5 (57-109)
Root/EP	96.8 ± 9.1 (76-123)	94.7 ± 8.0 (78-112)
Onset latency (milliseconds)		
Wrist	3.7 ± 0.4	2.8 ± 0.4
EP	11.8 ± 1.0	11.8 ± 1.1
Root	12.8 ± 1.0	12.6 ± 1.2
Root (laterality)	0.5 ± 0.4	0.3 ± 0.3
EP-Root	1.0 ± 0.4	0.7 ± 0.3

Data are shown as mean ± SD (range). ADM = abductor digiti minimi; CMAPs = compound muscle action potentials; EP = Erb's point; FDI = first dorsal interosseus; Root = cervical motor roots; SD = standard deviation.

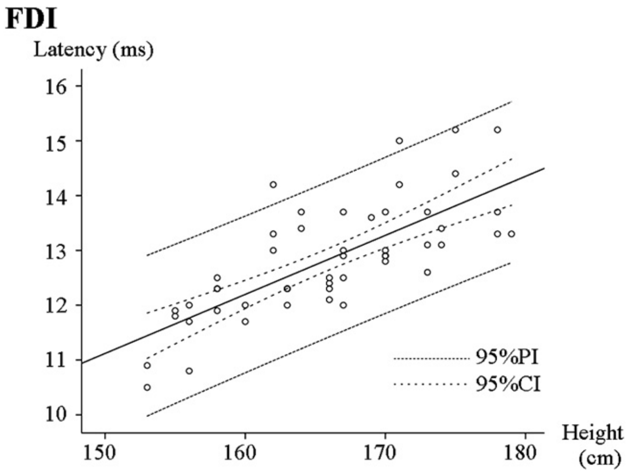

Figure 4 Significantly positive correlation between compound muscle action potential (CMAP) latency and body height. Data from the first dorsal interosseus (FDI) muscle are plotted. The formula for the relationship between latency and body height is as follows: latency = 0.11 × body height − 5.04 ($P < .001$, $R^2 = 0.55$). PI = prediction interval; CI = confidence interval.

wrist, below the elbow, and at the EP were all normal in amplitude, area, and latency. The supramaximal CMAP that occurred in response to MRS, however, had an amplitude that was obviously smaller than those of the other distal CMAPs. The amplitude of the CMAP in response to MRS was 40% of that of the CMAP in response to EP stimulation, which itself was smaller than the mean –2 SD (72%) of our normal values shown previously. Based on these results, we concluded that a conduction block was present between these two sites, that is, between the brachial plexus and the exit of the cervical spinal nerves from the intervertebral foramina. The patient's symptoms improved after treatment with intravenous immunoglobulin. After the symptoms had improved, the amplitude of his CMAPs occurring in response to MRS recovered to 96% of that of his CMAPS occurring in response to EP stimulation.

Discussion

The current data show that magnetic stimulation can be useful for evaluating conduction in the proximal regions of peripheral nerves as well as for central motor conduction studies. If this is confirmed, magnetic stimulation may come to be used in the diagnosis of neuropathies such as inflammatory demyelinating polyneuropathy,[8,9] brachial plexus injury,[10] and radiculopathy.[1,3,9] Magnetic or electrical stimulation over the cervical enlargements is often termed motor "root" stimulation, but neither method actually activates the spinal motor roots; instead, stimulation is delivered to the spinal nerves as they exit from the spinal canal through the intervertebral foramina.[2,4,11,12] Accordingly, "spinal nerve stimulation" would be a more correct nomenclature; however, because MRS has been commonly used, we use this term to describe our method in this article.

Several reports have demonstrated the clinical usefulness of data acquired through MRS, especially data on the latency of responses.[2,3,13,14] Data on the amplitude and area of responses, in contrast, have rarely been used as parameters for evaluation, probably because MRS cannot always elicit supramaximal CMAPs. The reported amplitudes of CMAPs occurring in response to MRS[2,3] have ranged from 10%-45% to 9%-100% and 16%-77% of the amplitudes of CMAPs occurring in response to peripheral nerve stimulation[4] in normal subjects. In our study, the amplitudes of CMAPs occurring in response to MRS ranged from 78%-100%. Moreover, supramaximal CMAPs could be obtained in 32 of 36 subjects, and the occurrence of supramaximal CMAPs in these subjects was verified by using high-voltage electrical stimulation. Our success in obtaining supramaximal CMAPs from most of the subjects might be explained by our use of a high-power magnetic stimulator that is about 1.4 times as powerful as commercially available stimulators. Another important technical point is that we pressed the coil firmly to the back of each subject while forcefully pulling the chest backward to place the coil as close as possible to the target spinal nerves.

Supramaximal stimulation is necessary for measurement of the CMAP amplitude in the detection of conduction blocks in neurophysiologic studies.[15,16] In the current study, the difference in amplitude between CMAPs in the ADM induced by EP stimulation and those induced by Root stimulation was about 6.5%; the highest normal limit (mean –2 SD) was 28%. This result is similar to one previously reported by Arunachalam et al.,[15] who conducted

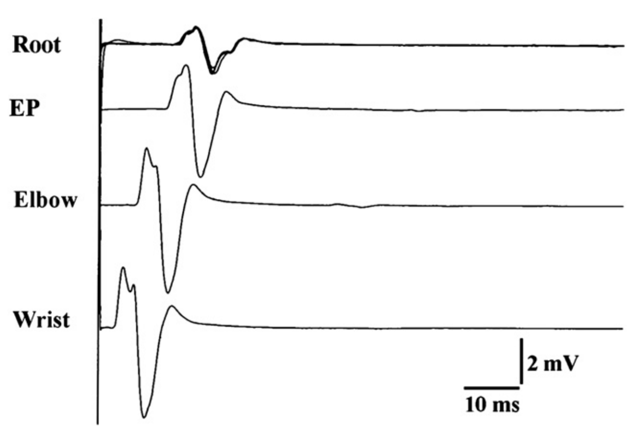

Figure 5 Compound muscle action potentials (CMAPs) in a patient with neuralgic amyotrophy. CMAPs from the right abductor digiti minimi (ADM) were elicited by means of electrical stimulation at the wrist, below the elbow, and at Erb's point (EP). CMAPs were also elicited by means of magnetic stimulation at the cervical motor roots (Root). The amplitude of MRS-induced CMAPs was only 40% of that of EP stimulation-induced CMAPs.

cervical motor root stimulation using a high-voltage electrical stimulator. Therefore, when supramaximal MRS is achieved and the difference in amplitude between CMAPs induced by EP stimulation and those induced by Root stimulation is above the highest normal limit, this indicates a conduction block, as in the case presentation.

The collision experiment revealed that volume conduction accounted for less than 9% of the responses in the FDI and less than 4% of those in the ADM. In the APB, however, volume conduction was substantially greater (by approximately 30%) than in the other two muscle. These amounts of volume conduction are similar to those previously reported in a study that used a high-voltage electrical stimulator.[15] The high-volume conduction commonly observed in CMAPs from the APB in response to both MRS and ERS is explained by the fact that the APB is surrounded by ulnar-nerve-innervated muscles (the flexor pollicis brevis and the adductor pollicis), as well as by the fact that APB itself is sometimes partly innervated by the ulnar nerve. Based on our results, we concluded that MRS-induced CMAPs from the APB are not suitable for amplitude evaluation.

A positive correlation between the latency of CMAPs occurring in response to MRS and body height has been reported.[3,13,17] Cervical motor root stimulation by means of a needle electrode has revealed an identical correlation.[18] Our normal values were consistent with these previously described values, and the formulas obtained through our study are useful for the evaluation of the latency of CMAPs in response to MRS.

ERS is an alternative method for cervical motor root stimulation, but magnetic stimulation offers two advantages over it. First, magnetic stimulation produces less discomfort than electrical stimulation, which can sometimes elicit severe pain. Second, magnetic stimulation can be used for patients on whose skin it is not possible to fix cutaneous electrodes because of skin problems.[19]

Our study has some limitations. First, the number of subjects was fairly small and their age range was fairly restricted; this makes it less likely that our data are normative. Data from additional healthy subjects must be acquired to make our data set comprehensive and normative. Second, supramaximal CMAPs cannot be obtained in all subjects. If CMAPs continue to enlarge as stimulation intensity increases, we cannot exclude the possibility of suboptimal stimulation. If this is the case, then amplitude inconsistencies in CMAPs occurring in response to MRS do not necessarily indicate conduction blocks in patient analyses. Another disadvantage of our stimulation method is the current spread to distal regions far from the expected stimulation point at very high stimulus intensities (such as stimulation with 95% or 100% maximal stimulator output). In this case, the existence of a conduction block may be missed because the stimulation site may jump to a more distal position lying beyond the region of the conduction block. Despite these limitations, however, MRS can provide us with useful information about proximal motor conduction when supramaximal CMAPs are obtained in response to MRS, as in the case study reported here.

This study has yielded two new findings with regard to MRS: (1) though previous studies have reported otherwise, supramaximal CMAPs can be elicited in response to MRS in most normal subjects. The amplitude and area of CMAPs can also be used as diagnostic parameters in patients who exhibit supramaximal CMAPs. (2) CMAP latency correlates significantly with body height; the formulas for this relationship have been provided.

Acknowledgments

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