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RIVIEW ARTICLE

REVIEW ON METHODOLOGY AND INTERPRETATION OF RESULTS OF MOTOR EVOKED POTENTIALS INDUCED WITH MAGNETIC FIELD OR ELECTRICAL STIMULI RECORDED PREOPERATIVELY OR INTRAOPERATIVELY

PRZEGLĄD METODOLOGII I INTERPRETACJI WYNIKÓW RUCHOWYCH POTENCJAŁÓW WYWOŁANYCH INDUKOWANYCH POLEM MAGNETYCZNYM LUB BODŹCAMI ELEKTRYCZNYMI REJESTROWANYCH PRZED- LUB ŚRÓDOPERACYJNIE

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ABSTRACT

Introduction

The method of motor evoked potentials recordings induced with magnetic field (MEP) (as part of the differential diagnosis of disease in the musculoskeletal system before the introduction of treatment) and motor evoked potentials induced with electrical stimuli (during intraoperative neuromonitoring) is particularly intensively used among clinical neurophysiology studies in the last twenty years.

Aim

The aim of the study is to review the practical usefulness of MEP in clinical diagnostics and present the most common examples of the application of this method, the possibility of modifications aimed at increasing non-invasiveness, safety and diagnostic precision.

Material and methods

The results of pilot tests of different variants of MEP recordings are presented preoperatively from muscles and nerves of the lower extremities in healthy volunteers (N = 10) and patients with disc-root conflicts (N = 15).

Results

Pilot tests show that in healthy people after oververtebral stimulation with the magnetic field at the lumbar level, the MEP amplitude and latency parameters recorded from nerves compared to those recorded from muscles are characterized by lower values (amplitudes by about 50%, latencies with mean at about 3 ms) and the time duration is increased by approximately 20%. The variability of MEP parameters is similar in patients with disc-root conflict in preoperative diagnostics, even though mean amplitude values from muscles were lower in comparison to healthy control group.

Conclusions

The MEP recording method from nerves vs. muscles after oververtebral stimulation with the magnetic field at the lumbar level in patients with disc-root conflict is diagnostically essential

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in cases of visible atrophic changes in muscles with symptoms of slight pathology in the transmission of nerve impulses in motor axons.

Keywords: motor evoked potentials, neurophysiological diagnostics, neuromonitoring, methodological modifications

STRESZCZENIE

Wstęp

Wśród badań neurofizjologii klinicznej ostatnich dwudziestu lat szczególnie intensywnie wykorzystywana jest metoda rejestracji ruchowych potencjałów wywołanych indukowanych polem magnetycznym (MEP) (w ramach diagnostyki różnicowej schorzenia w narządzie ruchu przed wprowadzeniem leczenia), jak i za pomocą impulsów elektrycznych (w trakcie neuromonitoringu śródoperacyjnego).

Cel

Celem pracy jest przegląd praktycznego wykorzystania w diagnostyce klinicznej MEP, przedstawienie najczęstszych przykładów aplikacji tej metody, możliwości modyfikacji mających na celu zwiększenie nieinwazyjności i bezpieczeństwa oraz podniesienia precyzji diagnostycznej.

Materiał i metody

Przedstawiono wyniki testów pilotażowych różnych wariantów rejestracji MEP, przedoperacyjne przy rejestracji z mięśni i nerwów kończyn dolnych u zdrowych ochotników (N = 10) oraz chorych z konfliktem krążkowo-korzeniowym (N = 15).

Wyniki

Testy pilotażowe wskazują, że u zdrowych ludzi po stymulacji nadkręgosłupowej polem magnetycznym na poziomie lędźwiowym, parametry amplitudy i latencji MEP przy rejestracji z nerwów w porównaniu do tych rejestrowanych z mięśni mają niższe wartości (amplitudy o około 50%, latencje o średnio 3ms) a czas trwania jest wydłużony o około 20%. Zmienność parametrów MEP ma podobny charakter u chorych z konfliktem krążkowo-korzeniowym w badaniach diagnostyki przedoperacyjnej, chociaż średnie amplitudy z mięśni są niższe w porównaniu do osobników zdrowych.

Wnioski

Metoda rejestracji MEP znad nerwów w porównaniu do mięśni po stymulacji nadkręgosłupowej polem magnetycznym na poziomie lędźwiowym u chorych z konfliktem krążkowo-korzeniowym ma znaczenie diagnostyczne w przypadkach widocznych zmian zanikowych w mięśniach z objawami niewielkiej patologii w przewodnictwie aksonów ruchowych nerwów.

Słowa kluczowe: ruchowe potencjały wywołane, diagnostyka neurofizjologiczna, neuromonitoring, modyfikacje metodyczne

Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that has been used for verification of the efferent transmission of neural impulses in cortico-bulbo-spinal pathways for diagnostic purposes (Merton and Morton, 1980; Barker *et al.*, 1985; Aglio *et al.*, 2002), while it's repetition with series of trains is used for both neuromonitoring (Huber *et al.* 2019; Charalampidis *et al.*, 2020) and therapeutic purposes (Danielewski *et al.*, 2015; León Ruiz *et al.*, 2018; Leszczyńska *et al.*, 2020).

Diagnostic significance

Neurophysiological diagnostics with MEP (motor evoked potentials) uses TMS with recordings of direct excitation of muscle motor units from cells of origin and fibers of corticospinal tracts and motor transmission in axons of upper and lower extremities' nerves (Hallet, 2000). However, when applied TMS stimulus strength exceeds 70–80% of the resting motor threshold (RMT; 0.84–0.96T), not only excitation but also inhibition of the spinal motor centres are observed (Hallet and Chokroverty, 2005; Oudega and Perez, 2012). This is due to the activation of not only cortical but also subcortical brain centres that influence the spinal cord circuits in a polysynaptic way, including connections via the inhibitory interneurons (Zhen and Chen, 2011). In human monosynaptic excitation of spinal motoneurons following applied TMS is described as very rare, di-or tri-synaptic excitatory and inhibitory connections are exerted from corticospinal fibers (Pauvert *et al.*, 1998), not only directly but with the use of propriospinal connections (Pierrot-Deseilligny, 1996; Nicolas *et al.*, 2001). The single, standard sinusoidal stimulus of 5 ms duration released from a circular coil of 12 cm diameter generates the magnetic field stream with the maximum limit of 2.4 T. When induced transcranially, it is possible that apart from the cortical structures, cells of origins of the rubrospinal tract in the midbrain are also excited, because of the stream penetration up to 5 cm deep (Oudega and Perez, 2012). The second possibility to study efferent transmission from the spinal level directly to the muscle is using TMS oververtebrally at the levels of certain neuromeres (Figure 1).

Combination of direct, transcranially indu-ced potentials and subtracted oververtebrally evoked, provides data about central conduction time of efferent impulses (Hallet and Chokroverty, 2005). Diagnostic importance of MEP application induced with TMS or at the spinal level has been presented in studies of patients with brain tumours resection (Deletis and Camargo, 2001), stroke (Nascimbeni *et al.,* 2006), myelopathy (Chan and Mills, 2005), radiculopathy (Bryndal *et al.,* 2019), traumatic brachial plexus injuries (Wiertel-Krawczuk and Huber, 2018), incomplete spinal cord injury (Leszczyńska et al., 2020) and facial paralysis (Kiya *et al.,* 2001).

Clinical relevance, limitations and future perspectives

TMS (with a single stimulus) and rTMS (with repetitive train of stimuli) seem to be safe methods of brain excitation and side effects are observed only in patients with epilepsy episodes and post-haemorrhaging stroke patients (Rossi *et al.*, 2009). Moreover, a methodological limitation may appear when motor evoked potentials are recorded in elder healthy subjects or patients with advanced muscles atrophy caused by axonal injuries (especially in disc-root conflicts). Healthy subjects aged 50–70 years usually display significant neurogenic changes in muscle motor units, influenced by sarcopenia, not especially caused by motor axons degenerative changes but with first visible signs of muscle mass reduction (atrophy) (Doherty *et al.*, 1993; Booth *et al.*, 1994). Patients with disc-root conflicts at the lumbosacral level may present degeneration of muscle motor units as a sequence of axonal degeneration from the level of compressed ventral root (Bryndal *et al.* 2019). However, after introducing conservative treatment, regenerative processes in motor fibers overtake new motor units formation, which explains that results of electroneurographic studies are better than electromyographic (Krarup *et al.*, 2002, 2016). Summarizing above, we suppose that motor evoked potentials recorded from nerves along their anatomical passage are more stable than recorded from muscles,

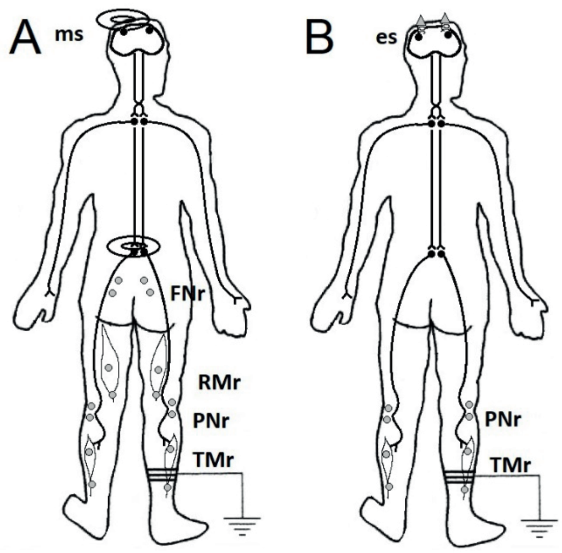

Figure 1. A picture illustrating location of stimulating and recording electrodes during studies of MEPs when (A) magnetic stimulus (ms) released from stimulating coil is applied transcranially or oververtebrally, as well as during MEPs recordings when (B) electrical stimulus (es) is induced transcranially with screw electrodes to depolarize motor cortex during intraoperative neuromonitoring. In A and B recordings can be performed with bipolar surface elecrodes from FN – femoral nerve, RM – rectus femoris muscle, PN – peroneal nerve, TM – anterior tibial muscle. s – stimulation, r – recording.

although, they can be characterized by lower amplitudes and shorter latencies parameters what comes from properties of nerves excitation.

Recordings of MEPs with surface electrodes instead needle electrodes including muscles and nerves combinations during neurophysiological monitoring associated with surgical interventions to the spine begin to make sense because of anaesthesiological influences and pediatric purposes (Figure 2).

The quality of MEPs recordings during intraoperative neuromonitoring from muscles can be significantly influenced by the depths of anaesthesia or muscle relaxants administration (Soghomonyan *et al.*, 2014), but not those recorded from nerves. There is a common agreement on the practical significance of MEPs recorded following transcranial electrical stimulation (TES) during surgical procedures (Figure 3A), especially when the MEPs recording station is located far beyond the exposed spine (Figure 3B).

The last issue was not studied with the application of transcranially induced electrical stimulus (rTES – repetitive transcranial electrical stimulation) in comparison to transcranially evoked with the magnetic stimulus (TMS). An overview of pediatric neuromonitoring databases do not show results of studies focusing on non-invasive approaches regarding MEPs recordings. It should be also remembered that during prolonged neurosurgical procedures, the natural, gradual attenuation of the signals may occur, more in children than adults and the origin of these changes remains unexplained (Soghomonyan *et al.*, 2014).

Aim

The study aims to present the preliminary results demonstrating practical usefulness of

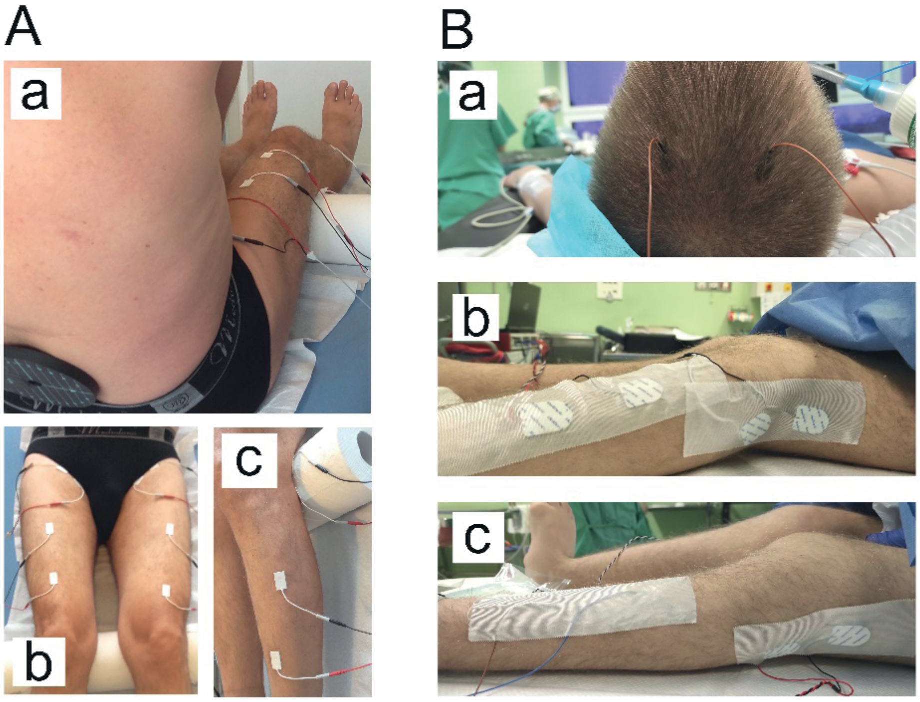

Figure 2. Photographs showing principles of stimulation and recordings variants during MEPs collections preoperatively (A) and intraoperatively (B).

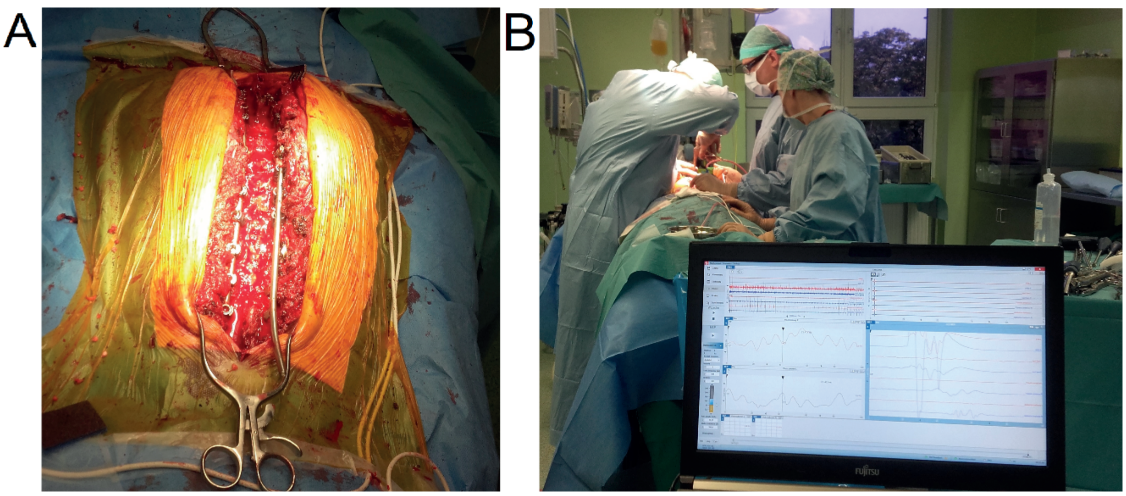

Figure 3. A – Photograph illustrating the operative area with exposed dorsal aspect of the spine from cervical (upper part) to lumbosacral (lower part) levels in one of the patients undergoing the surgical correction of scoliosis. B – The distance of the recorder's screen used for MEPs' intraoperative monitoring to the surgical bed on the surgical theatre.

MEP in clinical diagnostics with the examples of modifications, which may increase its non-invasiveness, safety and diagnostic precision. The hypothesis will be verified on similarities of MEPs recordings parameters from nerves vs. muscles of lower extremities in patients with disc-root conflicts preoperatively in comparison to same recorded in healthy subjects.

Materials and methods

The results of pilot tests of different variants of MEPs recordings have been presented preoperatively from muscles and nerves of the lower extremities in healthy volunteers in comparison to patients with disc-root conflicts. The sample included 10 healthy volunteers (control group) and 15 patients with disc-root conflict at lumbar level (L4-L5) preoperatively, aged from 17 to 70 years (average 43 ± 12 years) and from 24 to 85 years (average 53 ± 18 years), respectively. Both groups represented similar anthropometric properties like height and weight from 1.73 cm and 79.40 kg (control group) and 1.71 m and 77.29 kg (patients) on average (Table 1).

Table 1. Data on anthropometric and demographical parameters of healthy subjects and patients with disc-root conflict at lumbar levels under the study.

Parameter	Age [years]	Height [m]	Weight [kg]	BMI [kg/m2]
Control Group N = 10	17 – 70 43.4 ± 12.6	1.58 – 1.89 1.73 ± 0.10	52 – 115 79.40 ± 17.06	20.1 – 36.3 26.3 ± 4.8
Patients with disc-root conflict N = 15	24 – 85 52.80 ± 18.10	1.53 – 1.93 1.71 ± 0.10	60 – 105 77.29 ± 14.12	18.83 – 44.85 26.59 ± 6.34

The study was performed from spring to autumn 2018, carried out in the Department of Pathophysiology of the Locomotor Organs of the Poznan University of Medical Sciences, Poland. The results both in healthy volunteers and patients were anonymous by giving a number in a spreadsheet to the certain subject after deleting personal data. The study was approved by Bioethics Committee from the University of Medical Sciences (including studies on healthy subjects; decision No 696/2018). Informed consent was obtained from all subjects involved in the study.

The main inclusion criteria both in healthy subjects and patients were no head injuries, epilepsy episodes, cardiovascular diseases, psychical disorders, pregnancy, oncological episodes, the presence of a pacemaker or cochlear implants or strokes episodes. Patients were qualified for study basing on MRI evaluation showing compression of L5 roots mono- or bilaterally. All neurophysiological recordings in patients were performed during diagnostic studies ordered by surgeons from Wiktor Dega Ortophaedics and Rehabilitation Clinical Hospital in Poznań, Poland.

Neurophysiological studies included recordings of motor evoked potentials, following magnetic stimulation applied oververtebrally at L4, L5, while recordings were performed bilaterally from femoral nerve (FN), rectus femoris muscle (RM), peroneal nerve (PN), anterior tibial muscle (TM) both in patients and healthy subjects. The results were collected/recorded using the 8-channel KeyPoint Diagnostic System (Medtronic A/S, Skovlunde, Denmark). Standard disposable Ag/AgCl surface electrodes with an active surface of 5 mm² were used. The active electrode was placed on the muscle belly and the reference electrode on its distal tendon according to the Guidelines of European Federation of Clinical Neurophysiology, when recordings were obtained from the muscle and while recorded from nerves, the active electrode is placed higher than reference electrode. The ground electrode was located on the leg, near knee. The recorder's low-pass filter was set to 20Hz, high-pass filter to 10kHz and the time base at 10ms/D, the amplification of signals was set between 200–5000μV. A bandwidth of 10Hz to 1000Hz and digitalization at 2000 samples per second and channel were used during recordings. The resistance between the surface of electrode and the skin was decreased with electroconductive gel. The examination was performed in an air-conditioned room in a controlled room temperature with an average temperature of 22°C, in a supine position.

Motor evoked potentials induced with magnetic field were elicited oververtebrally with a single, biphase, lasting 5 milliseconds pulses to evaluate the efferent transmission of neural impulses from the spinal motor centres to nerves above their anatomical passage and the respective effectors innervated by them. The motor evoked potentials were be induced using circular coil C-100, with 110 mm of diameter, connected to a MagPro X-100 pulse generator (Medtronic). The maximum limit of the magnetic field stimuli was 2.4 T on the skin surface. The stream of the magnetic field elicited with the coil at the strength 70–80% of resting motor threshold (RMT; 0.84–0.96 T) excited all neural structures up to 3–5 cm deep. The final averaged recording was obtained from at least 3 stimulations performed using a single magnetic pulse with a strength of 60–75% of the maximal stimulus output. The parameters of amplitudes, latencies and MEPs durations recorded from nerves and muscles were analyzed. The amplitude was measured from peak to peak of the signal, the latency from the stimulus application marked by the artefact in the recording to the onset of potential, the duration from the onset of the potential to its end with reference to the isoelectric line.

Patients and healthy subjects did not report the stimulation as painless, but they felt the little spread of current to the lower extremities, they were always awake and cooperating.

Statistical analysis

Statistical analysis of obtained data was performed using Statistica 13 software (StatSoft, Poland). Descriptive statistics were presented as minimal and maximal values (range), mean or median and standard deviations (SD). Normative parameters were calculated based on the results obtained from healthy volunteers in the control group (Table 2). The Shapiro-Wilk test was used to assess the normality of distributions in the test score. T-Student test and mean values were used to evaluate changes for the depended groups. P-values of less than 0.05 were considered statistically significant.

Results

The comparative examples of recordings from one of the healthy control and a patient with disc-root conflict at L5 are shown in figure 4, while the presentation of gathered results is presented in table 2.

In general, both in the control group and patients, values of MEPs amplitudes recorded from nerves were at least half smaller than those recorded from muscles and all these differences were statistically significant except TM vs PN in patients. Due to the fact that electrodes recording signals from nerves are closer to the stimulation area along the neuronal impulses passage than those from muscles, it is evident that latencies should be shorter. As it was expected, the latencies appeared to be significantly shorter (all p values are much smaller than the level of significance $\alpha = 0{,}05$) in recordings from nerves than from muscles with a mean at about 3 ms. Both in control group and patients, durations recorded from nerves were observed to be few milliseconds longer than those recorded from muscles. Similar differences appeared in FN vs. RM in both groups of subjects (up to 10%) and in both groups they were statistically significant. In PN vs. TM all differences were significant at about 25% in healthy subjects in the patients group at about 12%.

In general, one of the most convincing indications for the stability of nerve recorded MEPs are shorter ranges of amplitudes than those recorded from muscles and also represented by smaller values of standard deviations.

Discussion

In 1988 Owen and co-workers first time have described and named „neurogenic MEPs", following electrical stimulation of spinal neuromeres with epidural electrodes for evaluation of motor transmission of neuronal impulses when recorded from nerves at popliteal fossa (Park and Hyun, 2015). Such an approach of MEPs recording was criticized by Deletis in 2001, because in his opinion, they correspond to the joined activation of motor and antidromically excited sensory pathways. The advantaged of such recordings are very rapid acquisition and resistance to most anaesthetics. Our recordings presented in this study is, up to our knowledge, the first description of oververtebrally induced MEPs with stable conditions when recorded from nerves. We have described the reference parameters recorded in a group of subjects of the healthy population which showed better

Table 2. Parameters of MEPs recordings obtained in control group of healthy volunteers and patients.

	Parameter	RM	FN	P	TM	PN	P
	MEP – Lumbo-Sacral Stimulation (preoperatively)						
Amplitude [µV]	Control Group (N = 10)	1000.00 – 4000.00	500.0 – 3000.0	**0.02**	1000.0 – 1500.0	300.0 – 2000.0	**0.0002**
		1905.00 ± 755.30	1405.0 ± 625.7		1165.0 ± 138.8	680.0 ± 390.6	
	Patients (disc-root conflict) (N = 15)	107.7 – 8000.0	100.0 – 1300.0	**0.008**	100.0 – 1500.0	107.7 – 2000.0	0.23
		1498.0 ± 2094.7	491.5 ± 391.5		402.0 ± 311.9	310.0 ± 414.6	
	p	0.4	**0.0000001**	NA	**0.0000000**	**0.003**	NA
Latency [ms]	Control Group (N = 10)	5.2 – 8.8	3.3 – 5.9	**0.0000000**	9.7 – 14.4	8.00 – 12.30	**0.0000000**
		6.7 ± 0.9	4.3 ± 0.8		12.0 ± 1.6	9.20 ± 1.07	
	Patients (disc-root conflict) (N = 15)	5.00 – 10.83	1.67 – 6.00	**0.0000000**	9.00 – 20.83	6.00 – 13.00	**0.0000000**
		7.62 ± 1.48	3.18 ± 1.14		13.92 ± 2.46	10.14 ± 2.00	
	p	**0.023**	**0.00043**	NA	**0.0036**	0.07	NA
Duration [ms]	Control Group (N = 10)	18.9 – 29.0	24.0 – 26.4	**0.015**	6.700 – 10.200	10.900 – 14.700	**0.0000000**
		23.9 ± 2.5	25.3 ± 0.8		8.060 – 1.015	12.955 ± 1.024	
	Patients (disc-root conflict) (N = 15)	16.67– 60.00	19.2 – 50.0	**0.0294**	16.00 – 45.00	20.0 – 47.3	**0.0302**
		27.91 ± 8.38	30.9 – 6.8		28.34 ± 7.13	32.2 ± 6.9	
	p	**0.046**	**0.0008**	NA	**0.0000000**	**0.0000000**	NA

Abbreviations: RM – rectus femoris muscle, FN – femoral nerve (femoral fossa), TM – tibialis anterior muscle, PN – peroneal nerve (popliteal fossa lateral part)

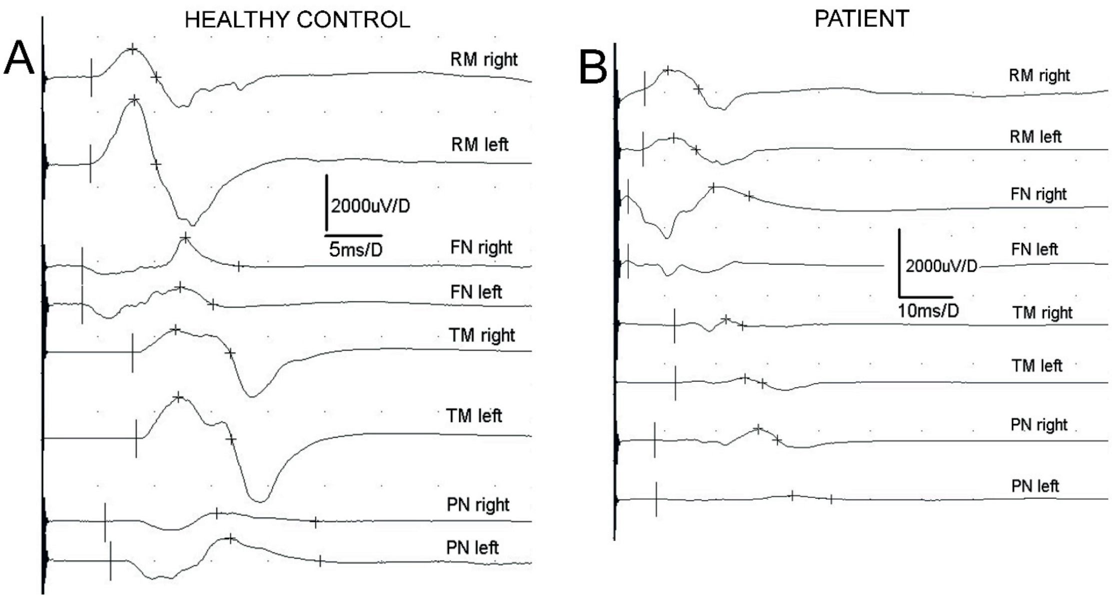

Figure 4. Examples of MEPs recordings in one of the healthy control and one of the patient group for comparison when performed from nerves and muscles following oververtebral stimulation. Note different time base of recordings in A and B, while the amplification of recordings is the same as indicated by horizontal and vertical bars, respectively.

parameters than those recorded in patients with disc-root conflict at L5. The results of this pilot study need confirmation on the larger populations of both healthy subjects and patients.

Conclusions

The MEP recording method from nerves vs muscles after oververtebral stimulation with the magnetic field at the lumbar level in patients with disc-root conflict is diagnostically essential in cases of visible atrophic changes in muscles with symptoms of slight pathology in the transmission of nerve impulses in motor axons. Such a MEPs recording methods is clinically valuable for the evaluation of patients at the certain step of rehabilitative treatment, when the conventional methods of motor function assessment fail.

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