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Non-invasive high voltage electrical stimulation as a monitoring tool of nerve root function in lumbosacral surgery

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HIGHLIGHTS

- High voltage electrical stimulation (HVES) is a non-invasive method, with unexpected, transient analgesic effects, able to safely reach maximal motor nerve root stimulation in patients with compressive radiculopathy.
- HVES allows reaching bilateral, simultaneous and maximal stimulation of lumbosacral roots at a level rostral to the operating field in lumbosacral surgery.
- The described technique is a sensitive tool to early detect conduction failure in manipulated lumbosacral motor nerve roots during surgery.

ABSTRACT

Objective: To verify the safety and clinical use of non-invasive high-voltage electrical stimulation (HVES) in patients with compressive radiculopathy. To test the feasibility of HVES to survey nerve root function during lumbosacral surgery.
Methods: In 20 patients undergoing lumbosacral surgery for degenerative spinal diseases, compound muscle action potentials (CMAPs) evoked by maximal HVES were bilaterally recorded throughout surgery from L3 to S2 radicular territories. A preliminary study was performed in awake patients to rule out detrimental effects caused by HVES.
Results: Preoperative study confirmed the safety of HVES. Unexpectedly, a transient but significant remission of pain was observed after root stimulation. Intraoperative monitoring (IOM) was accomplished in all patients. HVES never hindered surgical procedures and never caused mechanical damage within the operatory field. In 4 patients acute, highly focal and reversible conduction failure was promptly detected by HVES in radicular territories congruent with the root manipulated at that moment.
Conclusions: HVES is a safe and sensitive tool to monitor nerve root function in lumbosacral surgery.
Significance: The method is based on the assumption that any acute conduction failure occurring during surgery can be immediately and unambiguously detected by HVES if root stimulation is supramaximal and delivered rostral to the surgical level.

1. Introduction

Although the overall incidence of neurologic complications after lumbosacral spine surgery is generally low (Antonacci and Eismont, 2001), the consequences of these injuries are often disabling. Patients with increasingly complex spinal deformities where multiple levels are fused or patients already operated underlying surgical revision more than primary surgery are particularly at risk (Pateder and Kostuil, 2005). The most common deficit

Abbreviations: BS-11, Eleven Point Box Scale; CMAP, compound motor action potential; DNIC, Diffuse Noxious Nociceptive Inhibitory Control; $ETCO_2$, end-tidal CO_2; FHB, flexor hallucis longus; HVES, high voltage electrical stimulation; IOM, intraoperative monitoring; NMJ, neuromuscular junction; MMD, minimum/maximum area difference; MUAP, motor unit action potential; PL, peroneus longus; SL, soleus; TA, tibialis anterior; TMS, transcranial magnetic stimulation; VM, vastus medialis.

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is a foot drop from L5 motor root damage (Holland, 2008). These data emphasizes the need for an effective monitoring of motor nerve root function during lumbosacral surgery. Several IOM techniques are available, each of which have well known limits (Holland, 2008; Gonzalez et al., 2009). Continuous free-running electromyography (EMG) recorded from muscles innervated by nerve roots that are exposed to surgical manipulation is a commonly used procedure, mainly because it provides immediate data (Holland, 1998, 2002; Gunnarsson et al., 2004). However, spontaneous EMG discharges result from ectopic firing of nerve fibers that are hyper-excitable and partially depolarized but still functioning. If root injury proceeds to a more severe dysfunction, causing conduction failure, EMG discharges unavoidably stop, possibly giving an unreliable impression of recovery.

During procedures involving the pedicle, stimulus-triggered EMG assesses nerve root status by testing the stimulus threshold of the nearby motor root through a monopolar stimulator that is inserted into a pedicle hole or attached to a pedicle screw (Calancie et al., 1992, 1994; Raynor et al., 2002). Misdirected holes or screws that are close or adjacent to the nerve root will result in an abnormally low stimulus intensity needed to elicit CMAPs in muscles of the corresponding myotome. This is an elegant and effective method, but it is technically more demanding and time consuming. It also does not allow subsequent functional monitoring of the involved nerve root to promptly detect possible false negative results (Anderson et al., 2002).

A single electric shock of proper intensity, delivered by means of a dorsoventral montage at the proper vertebral level, customized to the individual subject, can safely achieve synchronous, bilateral, and maximal activation of the lumbosacral roots very close to their origin from the spinal cord (Troni et al., 1996, 2011a). This paper describes the application of high-voltage electrical stimulation (HVES) for IOM of motor nerve root function during lumbosacral surgery. The assumption is that, within the limits of the sensitivity of the method defined by the degree of stability of CMAP areas in serial recording, no conduction failure can escape root stimulation, provided that it is supramaximal and delivered above the level of surgical procedure.

Occasional but recurrent experience with the use of HVES in outpatients referring previous histories of back pain and/or compressive radiculopathy, consistently proving the absence of acute or late adverse effects induced by root stimulation, encouraged and legitimated this study. Results of this study have been previously presented in part in abstract form (Troni et al., 2011b).

2. Methods

2.1. Patient population

The study was performed on 20 consecutive patients undergoing surgery for degenerative lumbosacral spinal disease with the exclusion of obese patients (girth values >105 cm) and patients who, at the moment of preliminary neurophysiological examination, had significant back and/or radicular pain (BS11 >4) according to the Eleven Point Box Scale (Jensen et al., 1989). They were 11 males and 9 females, ranging in age from 40 to 77 years (mean: 59 ± 11). The study was conducted after approval by the local Ethics Committee. Written informed consent was obtained from all patients.

In all patients, the common clinical feature and the most frequent reason of surgical choice, was chronic or recurrent back pain and unilateral or bilateral radicular pain. Six patients had right (2) or left (4) L5/S1 spondylolisthesis and/or L5/S1 lumbar disc herniation with dysfunctional segmental motion. EMG showed severe (1), moderate (1), mild (4) neurogenic damage in S1 myotome. They underwent L5/S1 stabilization (2), L5/S1 microsurgical discectomy and stabilization (4) with left L5 hemilaminectomy in 2 of them. Seven patients suffered from lumbar spinal stenosis with dysfunctional segmental motion. EMG examination was normal in 3 and showed severe (1) or moderate (3) bilateral, although variable and asymmetrical, denervation in peroneal, calf and hamstring muscles. They underwent L3/L4/L5 laminectomy with decompression of nerve roots and L2 to S1 (2), L4/L5/S1 (3) and L3/L4/L5 (2) stabilization. Five patients had right (2) or left (3) L4/L5 lumbar disc herniation (3) or intra-extraforaminal disc herniation (2) with moderate (2) or mild (3) neurogenic damage in L5 myotome on EMG examination. They were treated with microsurgical L4/L5 discectomty, foraminotomy and L4/L5 stabilization. One male patient had right L3/L4 lumbar disc herniation with mild neurogenic damage in quadriceps and tibialis anterior muscles. He underwent microsurgical right L3/L4 discectomy. One female patient had a synovial cyst of left L4/L5 facet joints with chronic pain and moderate denervation on L5 myotome. She underwent hemilaminectomy and L4/L5 stabilization.

2.2. Preoperative study

The day before surgery, all patients underwent HVES of lumbosacral root in order (1) to evaluate the clinical safety of the technique in the awake patient before its use in the blind condition represented by the anesthetized patient during surgery; (2) to locate the optimal stimulation point over the vertebral column, customized to the individual patient, to reach a supramaximal and balanced stimulation of lumbosacral roots with the minimum current strength; (3) to test the use of extensive CMAP recording to map the distribution of neurogenic damage, as expressed by the reduction of CMAP areas, in different radicular territories.

Careful clinical examination was performed before, after the neurophysiologic study and in the following day, before surgery. Pain was evaluated (BS-11) immediately before examination with the patient lying in supine position and at the end of neurophysiological examination.

HVES was performed using a trans-abdominal stimulating montage (Troni et al., 1996). The cathode was a silver-silver chloride surface cup electrode (diameter 1 cm) placed at midline along the vertebral column, and the anode was a large round electrode (diameter 8 cm) placed midway between the umbilicus and the apex of the xiphoid process. Examination was performed with the supine patient after positioning of the multi-electrode probe.

According to the technique fully described elsewhere (Troni et al., 2011a), the optimal stimulation site was located by testing several stimulation sites of a multiple electrode array (7 silver–silver chloride cup electrodes, 1 cm of diameter, 1.5 cm apart, arranged in a rostral to caudal direction) placed over the dorsolumbar tract of the vertebral column. It was taped over the midline so that the 3rd electrode (labeled 0) corresponded to D12/L1 interspinous space, previously localized using the Tuffier's line that usually intersects the midline at the L4 spinous process or L4/L5 interspace. This arrangement ensured 2 stimulation sites rostral (+1 and +2) and 4 caudal (−1 to −4) to the supposed D12/L1 interspace. The procedure always started by stimulating at electrode 0. Current intensity was progressively raised until CMAPs of low amplitude were recorded in at least 3 or 4 of the 10 recording sites. Maintaining the same near-threshold stimulating current, the other more cranial and more caudal sites were tested. The optimal stimulation site was defined as the most rostral site that simultaneously evoked CMAPs in both proximal and distal muscles at the lowest threshold. As shown by MRI studies (Troni et al., 2011a, 2011b), the virtual axis joining the stimulating cathode to the ventral anode usually intersects the middle tract of the lumbar enlargement of the spinal cord, suggesting that the stimulating point reaches its maximal effectiveness when it is equidistant between the point of origin of the upper lumbar (L2/L3) and that of the upper sacral roots(S1/S2).

Then, current strength was progressively raised in 4–6 steps to achieve CMAPs of maximal amplitude in all recording sites. Just as for peripheral nerve stimulation, we considered a CMAP maximal when its size remained stable notwithstanding a further increase of stimulating current.

CMAPs were bilaterally recorded (bandwidth of 10–2000 Hz) with a pair of surface electrodes with a recording area of 54 mm^2 (Ambu®Neuroline 715) placed 5 cm apart over the muscle belly at symmetrical sites in a proximal to distal arrangement. The recording pattern was chosen to optimize the mapping of all lumbosacral myotomes with the exclusion of L1, clinically negligible, and S3/S4, which innervates the pudendal territory and presents specific challenges in prolonged recording that deserve further methodological study. The recording pattern included the vastus medialis (VM: L2/L3/L4); the tibialis anterior (TA: L4/L5); the peroneus longus (PL: L5/S1); the soleus (SL: L5/S1/S2) and the flexor hallucis brevis (FHB: S1/S2). Optimal and symmetrical recording sites (i.e., those providing motor responses of maximal amplitude with a clear-cut onset and a regular shape) were previously located after stimulation of the corresponding peripheral nerves: the femoral nerve at the inguinal groin (0.5 ms) for VM, the peroneal nerve at the fibular head (0.2 ms) for TA and PL, the tibial nerve (0.2 ms) at the popliteal fossa for SL and at the ankle for FHB.

The main purpose of this extensive recording pattern was to balance the overlapping muscle innervations and to compensate for the individual variability in motor root territories, so that mapping of a root was not depended on a single target muscle. Regardless of the labels, which refer to conventional recording points for individual muscles (Perotto, 2005), all CMAPs obtained with a wide recording area, unavoidably include some components, usually of much lower amplitude, from nearby muscles but usually belonging to the same myotome, due to a crosstalk mechanism. This is particularly true for the FHB CMAP, which includes components generated by the other plantar muscles (Troni et al., 2010), for the PL CMAP, which may be partly generated by the nearby TA and lateral gastrocnemius and for the SL CMAP, which necessarily includes activity from gastrocnemius.

Optimal stimulating and recording sites were marked with a dermographic pencil to facilitate the correct electrode placement in the operating room. A 16-channel bipolar amplifier (BrainAmpExG, Brain Products GmbH, Germany) was used for recording CMAPs and continuous EMG activity. Peripheral nerve stimulation was performed using a Digitimer DS7 stimulator (Digitimer Ltd.,

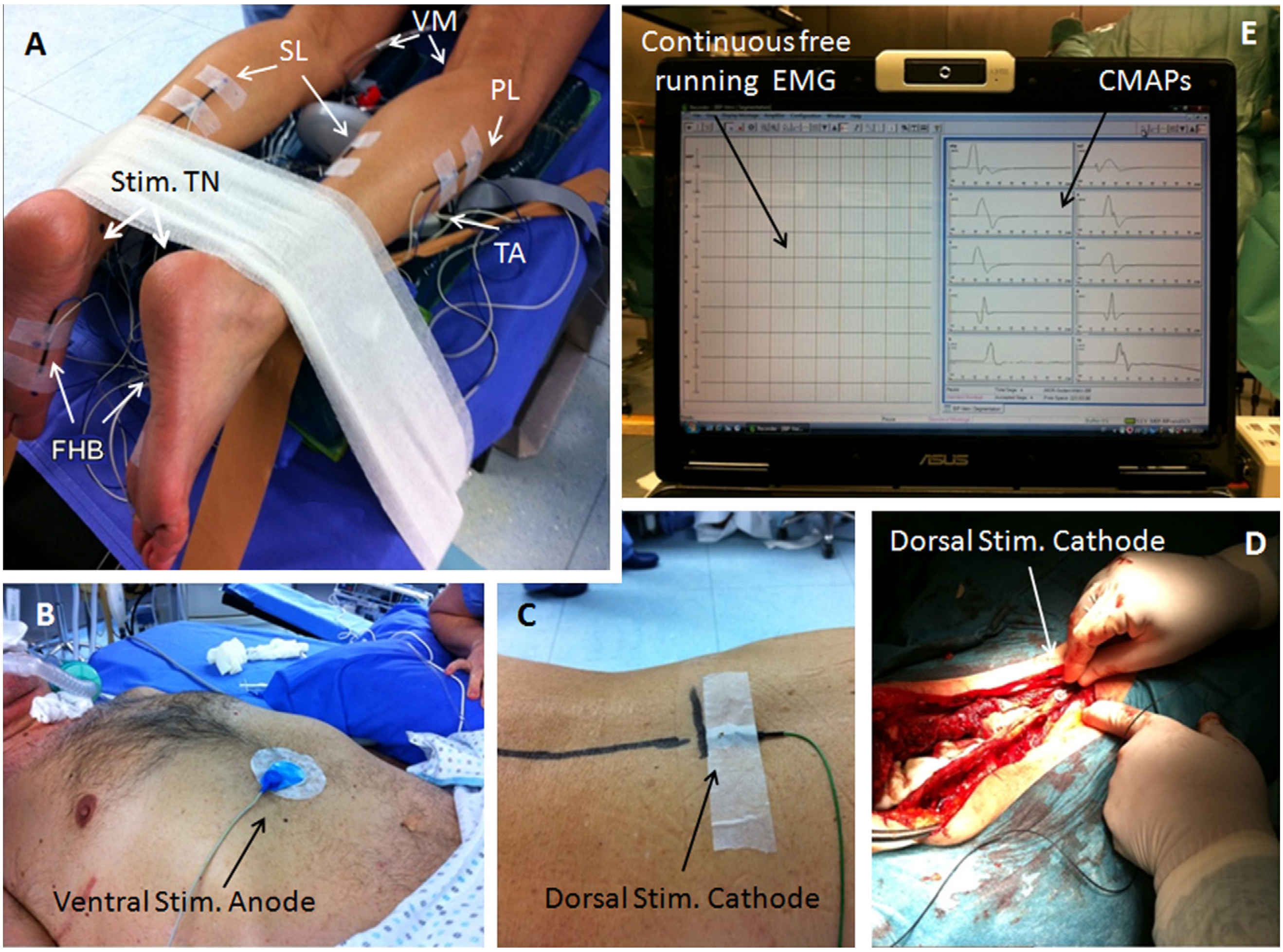

Fig. 1. IOM methodology. Maximal CMAPs were bilaterally recorded from the VM, TA, PL, SL and FHB muscles using sub-dermal monopolar (10 mm) needle electrodes (A) after maximal HVES using the dorsoventral montage. The cathode was a surface silver-silver chloride cup electrode. It was placed at the previously localized optimal stimulation site over the vertebral column. (C) The anode was a large, round surface electrode (8 cm) placed ventrally over the midpoint between the umbilicus and the tip of the xiphoid process. (B) In the two cases in whom the stimulation site was caudal to the upper border of the surgical incision, the stimulating cathode was included in the operative field and fixed to the interspinous ligament at a level corresponding to the surface point. Ongoing EMG activity was simultaneously recorded from all muscles throughout the surgical session. (E) The degree of NM blockade was monitored by delivering 4 maximal stimuli at 3 Hz to both tibial nerves at the ankle using subcutaneous needle electrodes. The repetitive trains of M responses were bilaterally recorded from the FHB muscles (A).

UK). HVES was performed using a high-voltage electrical stimulator, the Digitimer D 185-Mark IIa (Digitimer Ltd., UK). This device has a maximum output of up to 1000 V and a maximal current of up to 1000 mA, which produce a rectangular (50 μs) pulse shape with extremely rapid rise and fall times.

2.3. Intraoperative monitoring

The IOM methodology is shown in Fig. 1. In most cases, the stimulating cathode was a surface electrode placed over the site previously detected in the pre-operative study (Fig. 1C). In two cases where the optimal site was just caudal to the upper limit of the surgical incision, the stimulating cathode was included in the surgical field and fixed to the interspinous space at a level corresponding to the surface site (Fig. 1D). For practical reasons (quick electrode placement with the lowest and enduring impedance without need for skin preparation), sub-dermal monopolar needle (1 cm) recording electrodes (Bionen®) were used instead of the surface electrodes utilized in the pre-operative study (Fig. 1A), maintaining the same inter-electrode distance. In our experience, the two different recording techniques do not introduce significant changes in CMAP latencies, areas and shapes.

Electrophysiological monitoring included continuous multichannel recording of spontaneous electromyographic activity from the same 10 recording sites (Fig. 1E). Stimulus intensity providing supramaximal HVES was difficult to define in the first 30–40 min of surgery due to neuromuscular junction (NMJ) blockade. Later, the appropriateness of stimulus strength was determined (and monitored) based on amplitude saturation of all the recorded CMAPs and was definitely checked, when necessary, by delivering 2 stimuli, 50 ms apart (Fig. 2). The rationale of the double HVES technique is that a reflex (H) component in the recorded CMAPs due to submaximal motor nerve root stimulation, indistinguishable from the direct response on the basis of latencies, can be unambiguously detected by delivering two identical stimuli 50 ms apart due to the long recovery cycle of the indirect response (as compared to the very short refractory period of the motor nerve fibers). The short interstimulus time interval cancels the reflex component of the second CMAP and the degree of the amplitude reduction as compared to the first CMAP quantifies the degree of submaximal stimulation. On the contrary, two CMAPs of equal area demonstrate a supramaximal activation of motor nerve roots with complete occlusion of the H reflex (Troni et al., 2011a).

NMJ blockade was quantified by delivering 4 supramaximal stimuli at 3 Hz to both posterior tibial nerves at the ankle, using monopolar needle electrodes, and recording the repetitive trains of M responses from FHB muscles (Fig. 1). Alternatively, peroneal nerves were stimulated at the fibular head with recording from the TA muscles.

Specialized software (GeMS®: General Multi-trigger Stimulator, EMS, Bologna, Italy) was used to manage the different stimulating protocols (single and double HVES and repetitive stimulation) and to allow rapid switching from one protocol to another. Moreover, custom software was available to calculate CMAP latencies and areas immediately after recording.

Root HVES was performed throughout the recording session with immediate evaluation of individual CMAP areas and shapes and periodically intensified at the end of potentially hazardous or technically difficult surgical procedures such as pedicle drilling, screw or rod placement/stretching or when the loudspeaker announced the focal occurrence of spontaneous EMG discharges in a muscle territory that was compatible with the root involved in

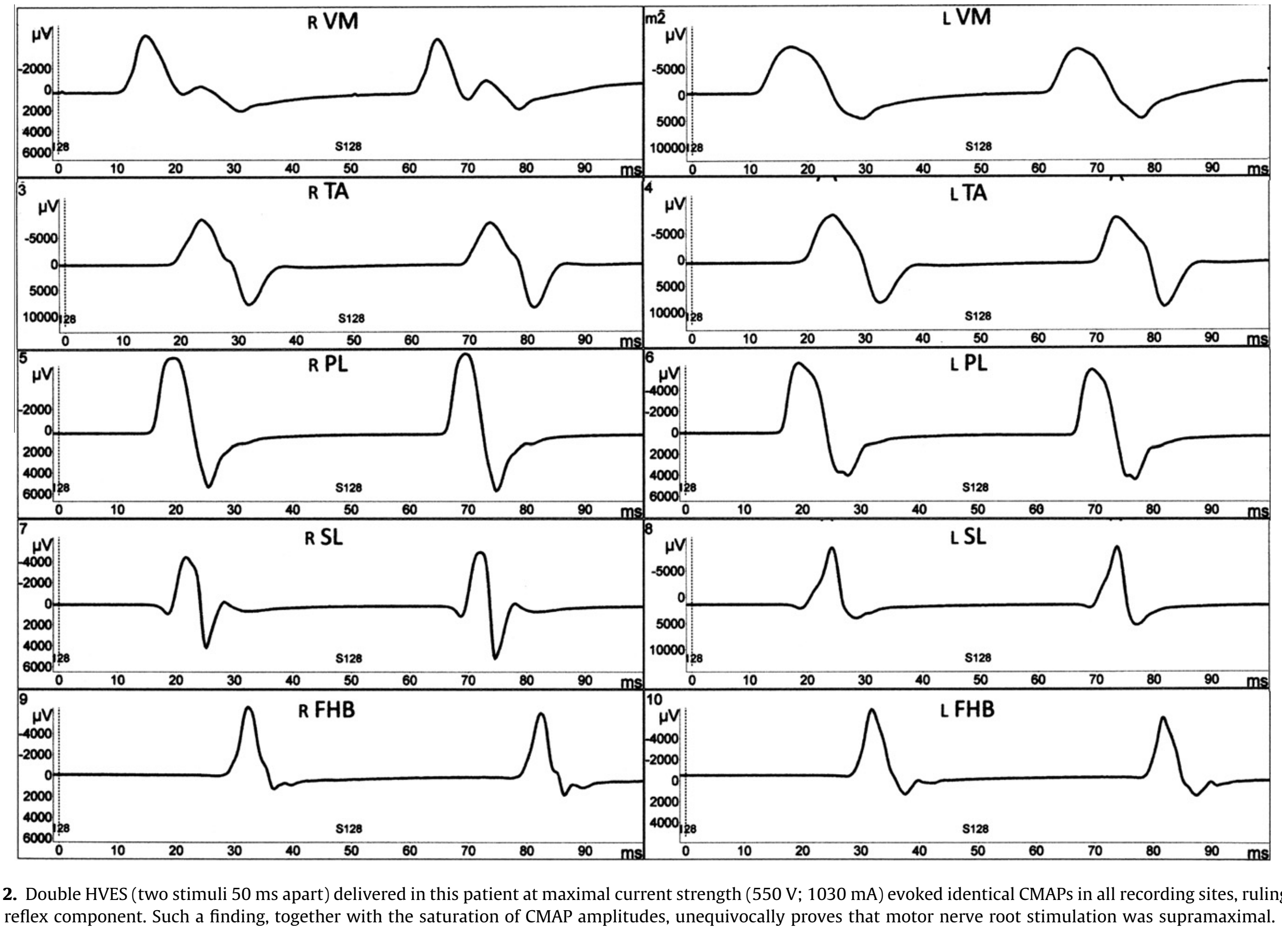

Fig. 2. Double HVES (two stimuli 50 ms apart) delivered in this patient at maximal current strength (550 V; 1030 mA) evoked identical CMAPs in all recording sites, ruling out any reflex component. Such a finding, together with the saturation of CMAP amplitudes, unequivocally proves that motor nerve root stimulation was supramaximal.

a surgical procedure. Stimuli were always delivered with permission or at request of the surgeons. Monitoring was discontinued just before the patient was awakened.

2.4. Anesthesia

Pre-induction was obtained with fentanyl (3–5 mg/kg). Induction of anesthesia was achieved with propofol (2 mg/kg). An intravenous mivacurium bolus (0.1 mg/kg) was used to facilitate endotracheal intubation, but no further neuromuscular blocking agents were administered afterward. Neuromuscular blockage was allowed to wear off to facilitate EMG and CMAP monitoring. Maintenance of anesthesia was obtained with sevoflurane (1.4% in an O_2 and air mixture). Intraoperative analgesia was maintained with an infusion of fentanyl (1 mg/kg/h) or boluses (50 mg/h). The patient was ventilated in intermittent positive pressure ventilation with a tidal volume of 8 ml/kg and a respiratory rate adjusted to an $ETCO_2$ between 34 and 38 mmHg. The arterial blood pressure, electrocardiogram (ECG) and level of O_2 saturation were continuously monitored in all patients.

2.5. Statistical analysis

Inter-side variability of CMAP areas was calculated in 20 healthy subjects, matched for age and sex, selected from our casuistry.

Variability of CMAP areas in serial recording could not be studied in awake patients in the preliminary study for practical and methodological reasons, such as the unacceptable number of painful maximal stimuli to be delivered for a period of time comparable to the duration of surgery and the absence of anaesthesia as a possible co-factor of CMAP variability. Critical analysis of all results showed in 4 patients a relevant deviation of some CMAP areas from usual behaviour in serial recording (see Results). The focal and reversible features of these changes and, above all, their strict temporal and anatomical correlation with the territory of the specific roots manipulated at that moment, legitimated ‘‘a priori’’ the suspect about their abnormal nature. So we discarded these 4 cases and used the remaining 16 patients as a material to calculate maximal normal CMAP variability.

CMAP variability in repeated intra-trial recordings, similarly to other neurophysiological parameters such as SEPs and MEPs, are likely to show a not Gaussian distribution; this suggests the use of nonparametric tests for assessing normal limits in healthy subjects. In the literature several nonparametric statistical analyses have been proposed, the most widely used being the 5th and 95th percentiles (Ravnborg et al., 1991). We first identified for each muscle, in each of the 16 ‘‘normal’’ IOM sessions, the two CMAPs with the extreme, minimum and maximum, area values between all responses recorded throughout the recording session, after recovery of NM blockade was complete. The percentage difference between them (MMD: Minimum/Maximum Difference) represents the 100th percentile of maximal area variability in each IOM session. The largest MMD among the 16 values was adopted as cut-off values to identify any significant area reduction for a given muscle.

Moreover, the cover the possibility of a Gaussian distribution of CMAP variability, mean ± SD of all MMD values was also calculated.

3. Results

3.1. Preoperative study

Preoperative HVES could be accomplished in all patients and location of the optimal stimulation site over the vertebral column was unambiguously obtained.

The mapping of CMAP areas to the maximal root HVES was generally in keeping with clinical and EMG findings. Overall inter-side variability of CMAP areas in our normal subjects, quite similar for all muscles, was 15 ± 18% (range 2–55%). CMAPs of reduced area were usually recorded in muscles of the involved myotomes. However, this finding was significant ($p < 0.05$) only in 2 of the 4 patients with the most severe neurogenic damage on EMG examination (Fig. 3).

We never found significant latency increases in CMAPs recorded from denervatedmyotomes.

Nerve root HVES was well tolerated in all patients. On the basis of the BS-11 scores, the discomfort induced by maximal HVES (BS-11: 5.8 ± 1.2) was similar to that previously observed in normal subjects (Troni et al., 2011a, 2011b). No side effects were observed either during or after the HVES. Clinical examination was unchanged.

Immediately before examination, 7 patients referred no pain (BS-11: 0), 7 had slight pain (BS-11: 1–2; mean: 1.7 ± 0.48) and 6 referred slight to moderate pain (BS-11: 3–4; mean: 3.3 ± 0.5). In no case did HVES induce pain in the 7 asymptomatic patients. Surprisingly, a transient relieve of pain, occurring almost immediately after examination was referred by 10 of the 13 symptomatic patients, including all 6 patients with the highest BS-11 scores (3–4). The mean pain reduction was 1.46 ± 0.8 of the BS-11 scale ($p < 0.001$ with the paired t test). Patients later reported that this effect lasted roughly from 2 to 4 h.

More importantly, in no case HVES caused a worsening of a preexistent neurological deficits and this was true both immediately after examination as well as throughout the time interval preceding surgery.

3.2. Intraoperative monitoring

Motor nerve root NIOM was completed in all patients. The current intensity needed to reach maximal root HVES ranged from 500 to 600 V (950–1100 mA). As expected, a lower intensity (650 and 700 mA, respectively) was needed in the two patients in whom the stimulating cathode was deeply fixed over the interspinous ligament during surgery. HVES induced a brisk but restrained jerk (see Discussion) and was never associated with dangerous movements of patients causing them to shift position on bolsters. As shown in Fig 1A, no patient needed to be restrained in specials ways.

The results of a complete motor nerve root monitoring performed in a surgical session in which no surgical and neurophysiological critical events occurred, as was the case in 16 of the 20 patients, are reported in Fig 4. The first part of surgery, corresponding to skeletonization, lasted on average approximately 25–35 min and was characterized by a progressive increase in the area of CMAP as the NMJ blockade wore off. A constant finding was a distal to proximal gradient of CMAP recovery, i.e., the CMAP increase was more rapid in the distal territories (FHB) compared to the proximal ones (TA, VM) as shown in Fig. 4(A–D).

When recovery from NMJ blockade was complete, root monitoring was characterized in all 20 patients, with the exception of the focal and transient abnormalities observed in 4 of them, by a remarkable stability of the area of all CMAPs throughout the surgical session with preservation of the individual shape of the different responses and the same was also true for the CMAPs of reduced amplitude due to a pre-existing neurogenic damage. Double HVES proved to be useful to confirm that root stimulation was persistently supramaximal (Fig 2). Maximal variability of CMAP areas in serial recording is represented in Table 1. Mean MMD values ± SD, cut-off values (mean + 3 SD; $p < 0.01$) and 95th percentiles of maximal variability are shown. Note that the upper values of the ranges represent the 100th percentile. All cut-off

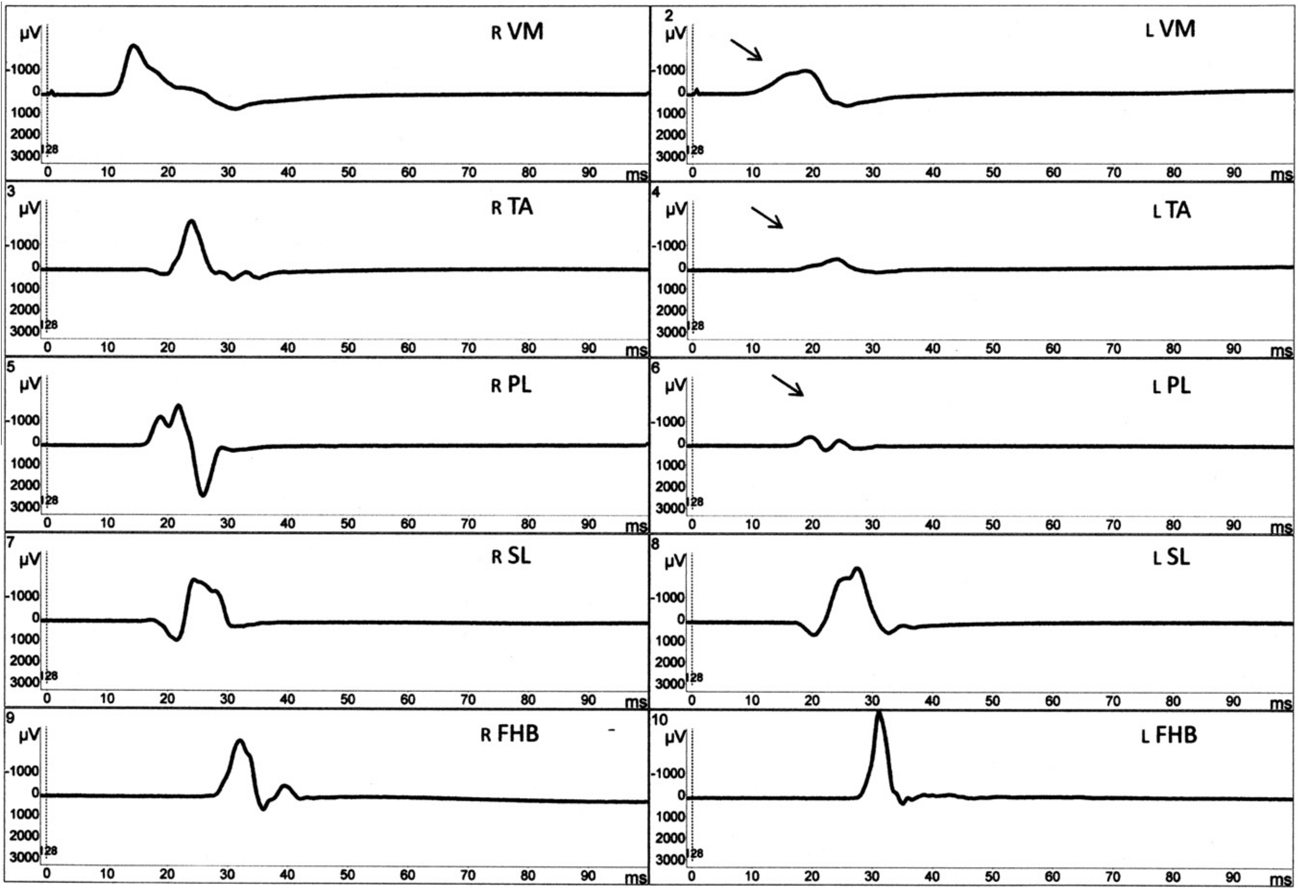

Fig. 3. Preoperative maximal CMAPs to HVES recorded in an individual patient. Note the significant ($p < 0.01$) reduction of the area of the left TA (80%) and PL (92%) CMAPs compared to the right side. This was in keeping with clinical findings and EMG examination, which showed neurogenic damage in left L4 and L5myotomes.

Table 1
Variability of CMAP area in serial recording during IOM.

	VM	TA	PL	SL	FHB
MMD (% ± SD)	7.5 ± 0.75	6.8 ± 0.66	8.2 ± 0.9	7.3 ± 0.89	8.7 ± 0.87
Range (%)	6.2–8.3	5.5–7.5	6.5–9.3	5.1–8	7–9.7
Mean + 3 SD (%)	9.75	8.8	10.9	10	11.3
95th Percentile	8.25	7.41	9.16	8	9.61

MMD: percentage difference between areas of the two CMAPs with the maximal and minimal values among all responses recorded throughout an IOM session. Note that the upper values of the ranges represent the 100th percentile of maximal CMAP variability observed in the patient sample.

values, parametric and nonparametric, are quite similar and indicate that a reduction of a CMAP area exceeding 10% is significant for all recording sites.

Spontaneous EMG discharges were observed, usually in the myotome innervated by the root manipulated at the same time that the spontaneous EMG occurred. They were always single motor unit action potentials (MUAP) or short bursts of MUAPs; more complex neurotonic or myokimic discharges were never observed. In the vast majority of cases, HVES, promptly delivered after the occurrence of spontaneous EMG bursts, failed to reveal any significant abnormality of the corresponding CMAPs.

In 4 cases, root HVES abruptly detected focal and transient CMAP alterations, without significant latency changes, suggesting an acute and reversible, although partial, conduction failure of the corresponding nerve root. The first, most relevant case is shown in Fig. 5. Toward the end of left L5 hemilaminectomy and foraminotomy, a clear-cut ($p < 0.01$) amplitude reduction in the left TA (75%) and, less importantly, in the left PL (30%) was detected by HVES (Fig. 5H). The onset of CMAP abnormalities was rapid; testing performed only 4 min before had shown totally unchanged responses. Subsequent monitoring, after the procedure was completed, documented a full recovery of both CMAP areas within 20 min (Fig. 5H–K). Scanty EMG discharges briefly preceded the CMAP abnormalities and also accompanied the recovery phase. In the second case, a significant CMAP fade (approximately 50%), involving the right PL and SL CMAPs, occurred at the end of right L4/L5 laminectomy. These changes rapidly recovered in about 8–10 min. Both the right PL and SL CMAPs, together with the left SL CMAP, were already significantly reduced due to neurogenic damage in the bilateral S1 and left L5 territories. In the third case, a rapidly reversible reduction in the CMAP areas occurred in the left TA (40%) and PL (45%) during a left L5 foraminotomy. Also, in this case, CMAP abnormalities occurred in muscles already suffering from significant neurogenic damage due to a pre-existing left L4/L5 radiculopathy (Fig. 3). In the fourth case a 30–35% reduction of right VM and TA CMAPs, completely reversed in 15–20 min after the end of root manipulation, was observed during right L4 foraminotomy.

The opposite phenomenon was never found, i.e., decompression of a nerve root was never associated with latency variations or with a rapid increase of CMAP areas that had been pre-operatively reduced due to pre-existing neurogenic damage.

4. Discussion

The use of maximal HVES in awake patients with radiculopathy was a severe but definitive safety test with a general implication. If no detrimental effects were seen in a clinical condition characterized by a mechanical impingement on nerve roots, the same is likely be true for any other pathological conditions affecting nerve roots. For obvious ethical and precautionary reasons we avoided using HVES in patients with significant pain at the moment of examination. However, unexpectedly, HVES not only never induced pain in asymptomatic patients or worsened pain in those symptomatic but it was associated with a transient improvement of pain in most patients of the latter group. Whether a mechanism similar to "pain relieved by pain" (van Wijk and Veldhuijzen, 2010), possibly due to activation of the Diffuse Noxious Nociceptive Inhibitory Control (DNIC; Le Bars et al., 1979), may have played a role in this serendipitous *collateral effect* of HVES in our patients is a fascinating hypothesis worthy to be specifically addressed.

Even more importantly, HVES never induced worsening of neurological deficits when present. This is in keeping with that lack of any mechanical detrimental effect on nerve root compression confirmed during surgery. HVES studies could be accomplished in all patients and were generally well tolerated. The pain induced by HVES in our patient group (BS-11: 5.8 ± 1.2) was not significantly different from normal subjects (Troni et al., 2011a, 2011b).

Although particular care was taken to locate the optimal recording sites, giving CMAPs with latencies and areas as symmetrical as possible, the inter-side variability of CMAP to root HVES is rather high for several reasons. The different CMAPs to root stimulation include complex cross-talk components from muscle groups not involved in distal stimulation. Moreover, the long conduction distance is associated to a greater physiological temporal dispersion with possible phenomena of electrical elision, which markedly affects the inter-side variability of individual CMAP areas, particularly in distal muscles (Troni et al., 2011a). This may explain the low sensitivity of the method as a diagnostic tool to map the distribution of neurogenic damage in our patients.

Within the limits of our casuistry, a significant latency increase was never observed in CMAPs recorded from affected myotomes. This is not surprising of one considers is that most radiculopathies are partial, leaving some fast conducting motor axons intact. This fraction of motor fibers, effectively and entirely stimulated by maximal HVES (but perhaps not recruited as F waves), provides the *true* minimum latency; moreover, a strictly focal conduction slowing at root level is likely to be lessened by the long conduction distances.

HVES in IOM proved to be feasible and safe; negative interference with surgery never occurred mainly because stimulation was always performed with the permission of the surgeon during a brief suspension of surgical procedure. No dangerous movements, no harmful effects on cardiac rhythm or on blood pressure were observed during either single or double HVES.

Healey et al. (2005) claimed that elevated paraspinal muscle activity could compress the intervertebral discs and possibly worsen nerve root impingement. Because maximal HVES causes a brisk jerk due to maximal activation of all lumbosacral roots, it is theoretically possible that a massive muscle contraction involving the

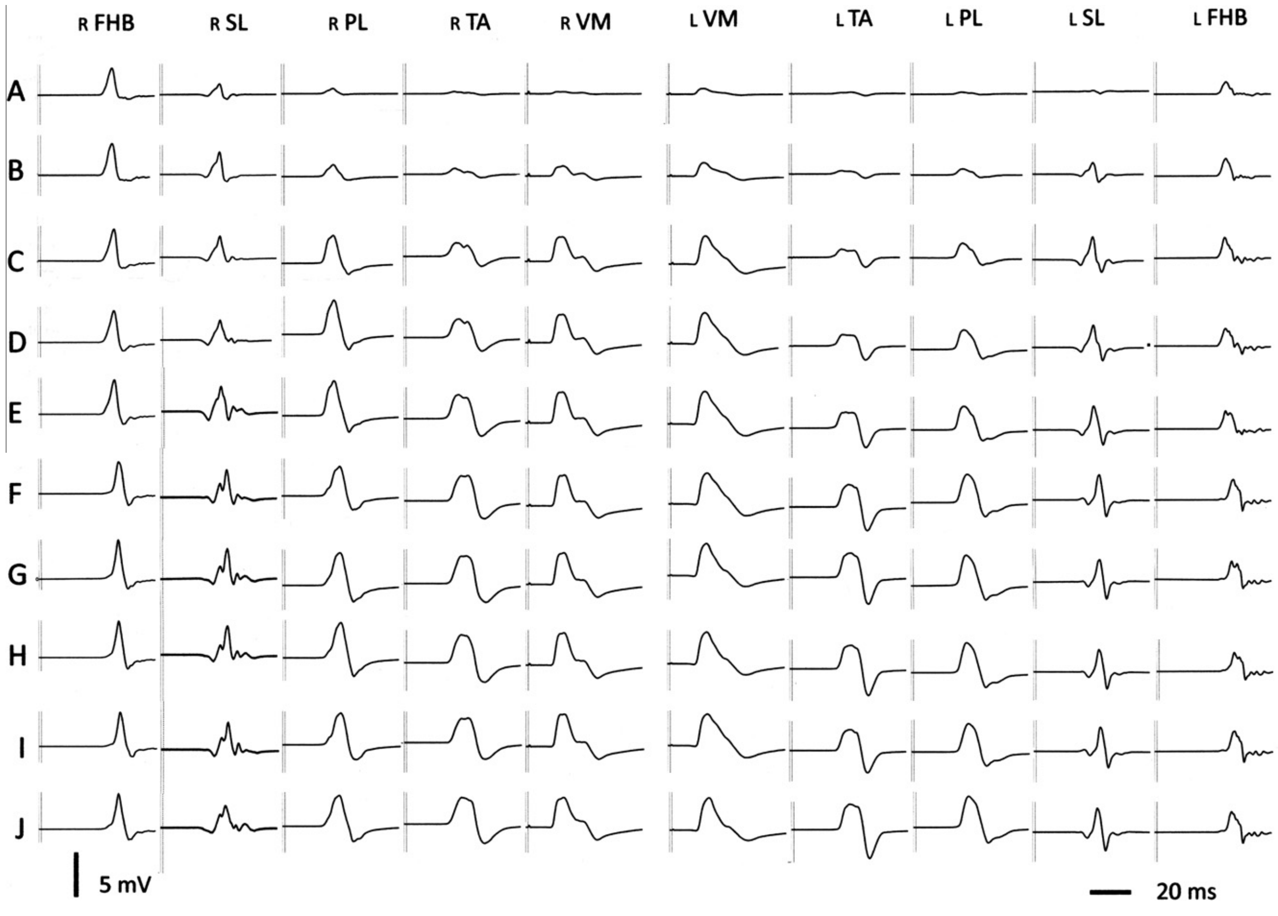

Fig. 4. Motor nerve root NIOM during a surgical session in which no critical events occurred. Note the initial, clear-cut reduction of CMAP amplitude due to NMJ blockade (A), which wore off in approximately 30 min (B–D). Usually, the degree of NMJ blockade was greater and the rate of wearing off was slower in proximal muscles (VM, TA) compared to the most distal ones (FHB). Some examples of maximal CMAPs elicited during and after relevant surgical procedures are shown: right L4 pedicle drilling (D) and screw placement (E), right S1 pedicle drilling (F), left L5 screw placement (G), end of right (H) and left (I) L5/S1 foraminotomy. Monitoring was continued until the completion of skin suturing (J). Note the remarkable stability of latency, amplitude and shape of individual CMAPs throughout the surgical session once NM blockade had worn off.

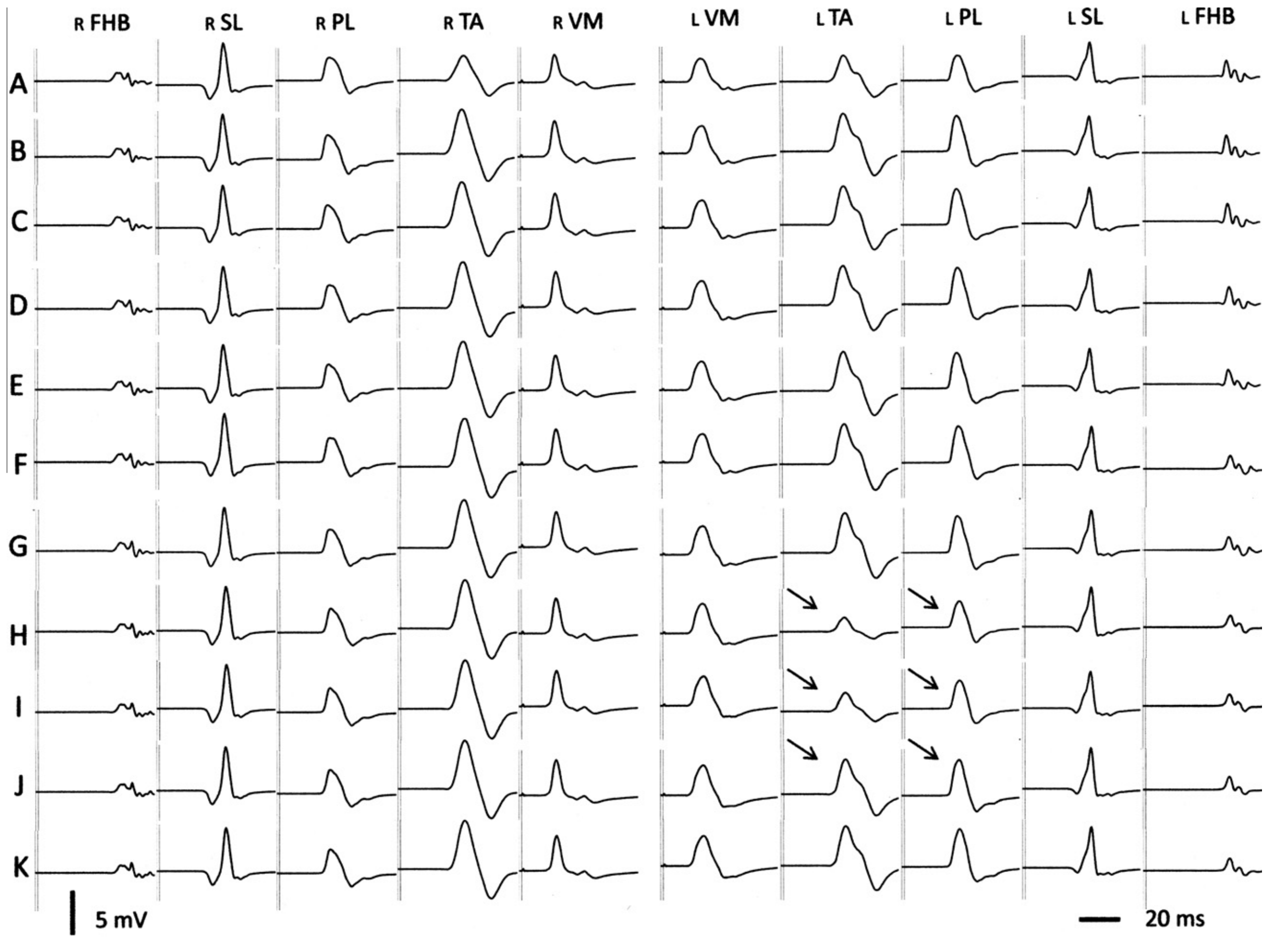

Fig. 5. Acute and reversible left L5 motor root dysfunction at the end of left L5 foraminotomy in one patient. Wearing off of NM blockade, not shown in the figure, was almost complete approximately 30–40 min after the beginning of surgery. No CMAP abnormalities were observed after right L5 pedicle drilling (A) and screw placement (B); after right S1 pedicle drilling (C) and screw placement (D); after left L5 (E) and left S1 (F) pedicle drilling and screw placement (G). At the end of left L5 laminectomy and foraminotomy, a marked ($p < 0.001$) and selective reduction of the area of the left TA CMAP and, to a lesser extent, of that of the left PL was observed (H). A complete recovery of CMAP areas occurred in the following 15–20 min (I, J). No other abnormalities were observed until the end of the surgical session (K).

paraspinal muscles can induce harmful effects on roots often already damaged by a pre-existing chronic compressive injury. Careful visual inspection during intra-operative single and double HVES never resulted in mechanical effects suggesting a squeezing action of paraspinal muscles on the vertebral column. This is not surprising because the bilateral muscle jerk induced by HVES was massive and brisk but also restrained. The force produced by a single muscle twitch is much lower than that produced by a tetanic or subtetanic contraction elicited by repetitive stimulation or voluntary contraction. In the awake subject, a more vigorous and prolonged muscle jerk may be obtained with TMS of the motor cortical area of the lower limbs during voluntary facilitation, particularly by using the double cone coil, probably due to repetitive firing of spinal motorneurones induced by TMS (Day et al., 1987).

All recorded CMAPs, in absence of any critical events, were characterized by a noteworthy stability of latency and area with remarkable preservation of individual shapes, and this was also true for the CMAPs of reduced amplitude due a preoperative neurogenic damage. Latency variability was negligible. In practice, the occurrence of a CMAP area reduction exceeding normal variability, i.e., greater than 10%, must lead first to verify the appropriateness of the stimulating intensity to rule out a submaximal stimulation, effectively checked in our experience with the double HVES technique, although a strictly focal alteration allows in itself to exclude this possibility.

Using the dorsoventral montage, HVES activates nerve roots at their very onset from the spinal cord or quite near to it (Troni et al., 2011a). A distal shift of the activating site through the operating field or even distally to it, due to current shunting to instruments, pedicle screws etc. can be reasonably ruled out for several reasons. It is theoretically and practically unlikely that erratic and unpredictable current flows, emerging from the stimulating cathode and deviating from the main stream directed toward the ventral anode, may jump the operating field and maintain distally, at a distance up to 10–15 cm, a stimulating power so high and constant to evoke in all recording sites CMAPs of stable and persistent maximal amplitude throughout surgery without any latency change, as shown in Fig. 4 and 5. A jump so remarkable of the real cathode with root activation at the neuroforamina or even more distally, as it usually happens with conventional magnetic coils, would result in a latency reduction up to 3, 4 ms as compared to our basal values (Troni et al., 2011a, 2011b). The same stability of CMAP latency and areas was also observed in the 2 patients in whom the stimulating cathode was deeply inserted at the rostral border of the operatory field. Moreover, a distal shift of the real cathode in our patients during surgery is not consistent with the fact that latencies, areas and shapes of all CMAPs were similar to that recorded in the same patient in the pre-operatory study where possible current shunting due to instruments, pedicle screws etc. can be ruled out.

The CMAP alterations observed in our 4 patients are not a technical artifact. Submaximal root activation could be ruled out and these focal alterations were observed in the myotome innervated by the root that was being manipulated at that moment. In all cases, these reversible CMAP changes were observed during or, more frequently, at the end of a surgical procedure involving a specific root, suggesting that the mechanical stress suffered by the root played a causal role. In all cases the TA and PL CMAPs have been the most frequently involved motor responses. This seems to confirm the L5 is the nerve root most at risk in lumbosacral surgery (Holland, 2008).

These acute abnormalities are felt to truly reflect a partial and transient conduction failure occurring in the manipulated root. This finding has not been described to date probably because a technique suitable to detect it was not yet available. The prompt reversibility of CMAP alterations in all our cases rules out any structural damage and strongly suggests the occurrence of the mildest type of conduction failure, i.e., a conduction block probably resulting from an electrolytic imbalance at the node of Ranvier. Acute disruption of blood-nerve barrier has been demonstrated in an experimental animal model of acute arterial ischemia and venous congestion at the lumbar nerve roots, by Kobayashi et al. (2009). Compressed nerve roots due to spinal canal stenosis frequently show gadolinium enhancement. This effect, first reported by Jinkins (1993), suggests edema of the nerve root and confirms a breakdown of the blood-nerve barrier. Burke et al. (2004) emphasized that, when the safety margin for impulse conduction is impaired by a disease process (as is probably was the case in most of our patients), normally innocuous fluctuations in membrane potential due to activity, slight trauma, transient ischemia or temperature fluctuations, can acutely jeopardize action potential generation. In this situation, even gentle and short manipulations may have significant effects if nerve roots have already been damaged by pre-existing degenerative pathology of the spine. The observed CMAP changes, although mild and reversible, are likely to reflect the early state of a nerve injury that could eventually lead to structural damage if lasting for a sufficiently long period of time. Such episodes of transient conduction failure, innocent in most cases, are probably fairly common and would have gone totally unnoticed due to the absence of any post-surgical clinical consequences. Nevertheless, in our opinion, their prompt detection is important mainly because the initial neurophysiological picture of a more serious and lasting root injury is likely to be the same, with the obvious main difference of the lack of any CMAP recovery at the end of surgery. In other words, the innocent nature of a CMAP abnormality can be only established "a posteriori". Moreover, immediate detection of early electrophysiological signs of nerve root distress is the necessary methodological premise to reliably test any present or future therapeutic approach, preventive measure or possible surgical strategies suitable to reduce the risk of root damage.

May the immediate awareness of an ongoing root dysfunction detected in our 4 patients, prompting the surgeon to reduced as much as possible, depending on the surgical needs, the duration of the mechanical stress suffered by the root, have played a role in the favourable evolution of the electrophysiological abnormalities? We are obviously not able to give an answer.

Most importantly, we at present do not know the degree and duration of a CMAP failure representing the border between reversible and irreversible root dysfunction. Extensive clinical application of the method will be needed to reliably define this crucial point.

A rapid, albeit partial, return of function immediately after surgical decompression in some cases of entrapment neuropathy and spondylotic myelopathy has been reported by Ishida et al. (2003). However, within the limits of our patient sample, we never observed a sudden increase in CMAPs that were reduced to baseline after successful decompression of the corresponding nerve root. This is not surprising because root pathology in chronically compressed nerve roots in degenerative diseases of the spine mainly consists of focal structural damage to nerve fibers (primarily to axons with a component of myelin damage as well). In this type of pathology, recovery so rapid as to occur during the short time period of intra-operative monitoring is hardly conceivable.

Spontaneous EMG discharges frequently occurred in the expected myotomes, reflecting irritation of the manipulated root. However, in the vast majority of cases, EMG discharges were not associated with any CMAP abnormality when nerve root function was checked by HVES. This finding confirms that EMG monitoring, as theoretically predictable, has a very high sensitivity in detecting an "irritative" nerve root dysfunction, i.e., a nerve fiber hyperexcitability, but a low specificity and efficacy in detecting a more severe, although still reversible damage leading to a conduction block (Holland, 1998, 2008; Gunnarsson et al., 2004). This suggests that continuous EMG monitoring provides useful warnings that should prompt an immediate assessment of nerve root function by HVES. However, it is well recognized that severe nerve damage, usually after sharp transaction, is not necessarily preceded by a phase of fiber hyper-excitability that produces EMG discharges (Holland, 2008). Therefore, root monitoring should be regularly performed during critical surgical procedures, regardless of the presence or absence of EMG abnormalities. Obviously, the method cannot immediately reveal the nature of the underlying pathology that is causing conduction failure. However, prompt, intensive monitoring can provide reliable clues, and it may be possible to quickly infer the nature of the injury based on the short-term evolution of electrophysiological abnormalities. Our preliminary clinical results seem to confirm the reliability of these expectations.

In conclusion, motor nerve root IOM using HVES is feasible and safe and is compatible with general anesthetics, the only interfering factor being NM blockade. It does not require averaging techniques. A few seconds are needed to deliver the stimulus and to evaluate the immediately available results. Monitoring is limited to motor nerve roots. However, to our knowledge, selective injury of the dorsal sensory nerve roots during lumbosacral surgery has never been reported.

Our technique is fully compatible with all other monitoring techniques. It includes continuous recording of spontaneous EMG activity. In particular, it may complement the stimulus-triggered EMG technique (Calancie et al., 1992, 1994; Raynor et al., 2002 Gonzalez et al., 2009), which specifically checks the appropriateness of individual pedicle hardware, by providing a subsequent functional monitoring of the involved nerve roots.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study of the findings specified in this paper.

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