Isoflurane-induced attenuation of motor evoked potentials caused by electrical motor cortex stimulation during surgery

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Dysfunction of spinal motor conduction during surgical procedures may not be reflected by changes in somatosensory evoked potential waveforms. A method of monitoring that allows direct and continuous assessment of motor function within the central nervous system during surgery would be useful. This paper describes one such method utilizing noninvasive electric cortical stimulation to evoke muscle activity (the motor evoked potential, or MEP) during surgery. The effect of isoflurane (superimposed on a baseline of N2O/narcotic anesthesia) on MEP's in response to cortical stimulation is specifically examined.

Eight patients undergoing elective neurosurgical operations were included in the study. All patients received a background of general anesthesia and partial nondepolarizing neuromuscular blockade. The motor cortex was stimulated electrically via self-adhesive scalp electrodes. Electromyographic responses from multiple muscles were measured with subdermal electroencephalograph-type needle electrodes. Motor responses to stimulation were continually recorded on magnetic tape for off-line analysis. Once closing of the surgical incision was begun, a series of four to five stimuli of constant magnitude were applied to obtain "baseline" MEP responses. Patients were then ventilated with isoflurane for up to 8 minutes, during which time stimuli were continued every 15 to 20 seconds. Comparison was made of MEP responses for trials before, 1 minute after, and 5 minutes after the addition of isoflurane.

All patients demonstrated reproducible motor responses to cortical stimulation during surgery. Addition of isoflurane ([isoflurane] = 0.5%) to pre-existing anesthesia caused marked attenuation of MEP amplitudes in all patients within 5 minutes of its application, without affecting neuromuscular transmission as judged by direct peripheral nerve stimulation. It is concluded that: 1) monitoring motor system integrity and function with electric transcortical cortical stimulation during surgery is feasible when utilizing an N2O/narcotic anesthetic protocol; and 2) the quality of data obtained will likely suffer with the addition of isoflurane.

KEY WORDS: evoked potentials, isoflurane, electrical stimulation, spinal cord, intraoperative monitoring, electromyography

In order to minimize the incidence of complications during spine surgery, some clinical tests of central nervous system (CNS) function have been used in the operating room to serve as "early warning systems" of potential nerve injury. For the most part, this intraoperative monitoring has relied heavily on somatosensory evoked potentials (SSEP's). However, there have been cases reported where SSEP signals did not change significantly from baseline values during spine surgery, yet the patients awoke with debilitating motor deficits. These complications indicate that SSEP testing during spine surgery should ideally be supplemented by more direct motor testing.

Such motor testing is possible through noninvasive stimulation of the motor cortex, leading to short-latency muscle contraction in the extremities. We refer to the resultant electromyographic (EMG) waveform from a given muscle as the "motor evoked potential," or MEP. Methods for stimulation involve either an intense and brief electrical current applied directly to the scalp or a pulsed magnetic field which induces a flow of electrical current in the cortex. Both methods have recently been used in the operating room during spine surgery.

To understand the strengths and weaknesses of this method of monitoring the motor systems, it is necessary
to determine how CNS and neuromuscular responsiveness to stimulation is affected by the different anesthetic regimens commonly in use. In this study, we superimposed isoflurane on pre-existing N2O/narcotic anesthesia in order to examine the effect of this drug on MEP responses to noninvasive electrical stimulation of the motor cortex during various surgical procedures involving the spine and spinal cord.

Clinical Material and Methods

This study was approved by the University of Miami Investigational Review Board, and an Investigational Device Exemption was granted by the United States Food and Drug Administration to one of the authors (B.C.) for use of the Digitimer stimulator in this study.

Patient Selection and Management

Patients undergoing spine surgery were recruited for this study. The informed consent of each patient was required before administration of the preoperative medications (2 to 4 mg midazolam and 0.2 mg glycopyrrolate). Table 1 summarizes the relevant data for the eight patients. The patients in this study served as their own controls, therefore, random assignment of patients to separate groups was not necessary. The selected patients had no history of head injury or seizures. As we were interested in examining MEP properties for a variety of procedures, we selected our patients with that object in mind.

All patients received general anesthesia (thiopental sodium, 4 mg/kg) combined with a muscle relaxant (vecuronium, 0.1 mg/kg, or succinylcholine, 1.5 mg/kg) for tracheal intubation. Anesthesia was maintained with nitrous oxide:oxygen (typically 60:40%) and a narcotic (fentanyl or sufentanil). Ventilation rate was typically 8 breaths/min. In two patients, low levels (0.2 vol%) of isoflurane (Case 4) or enflurane (Case 2) were used to help control anesthetic depth and blood pressure. Partial neuromuscular blockade was maintained by intermittent bolus injections of vecuronium bromide or by constant infusion of atracurium bromide.

Neuromuscular blockade was assessed by two methods: 1) train-of-four electrical stimulation (0.5 Hz) of the ulnar or facial nerve, and observation and palpation of the resultant twitches; and 2) supramaximal stimulation of the median or posterior tibial nerve and recording of the EMG M-wave from the thenar muscle group or abductor hallucis muscle, respectively. Median or posterior tibial nerve stimulation followed each cortical stimulus after a delay of 2.0 seconds; a two-channel stimulator was used, of which channel 1 triggered cortical stimulation and channel 2 (train output) stimulated the peripheral nerve. We attempted to maintain neuromuscular blockade at a level producing at least two twitches to the stimulus train. For median or posterior tibial nerve stimulation, this level of blockade typically corresponded to an M-wave 10% to 20% of the unblocked amplitude for the first stimulus pulse, although in some cases blockade was less developed at the time of study. Oxygen saturation, end-tidal CO2, end-tidal isoflurane, nasopharyngeal core temperature, heart rate, and systolic, diastolic, and mean arterial blood pressures were continuously monitored in each case and judged to be within normal limits throughout the study. The SSEPs were also continuously monitored with standard procedures.

Cortical Stimulation and Electromyography

Three recording sites were measured and marked on the scalp, 1 cm anterior to the standard electroencephalographic (EEG) recording sites of C3, C4, and Cz. These sites are referred to herein as C3*, C4*, and Cz*, respectively. It was determined in a previous study that stimulation between C3* and Cz* (anode and cathode) and between C4* and Cz* caused selective activation of muscles in the right and left forearm and hand, respectively (see also Day, et al.4). Reversing the polarity between either C3* to Cz* or C4* to Cz* (that is, making Cz* the anode) results in selective activation of lower-extremity muscles at threshold.

A patch of hair approximately 3 cm square was shaved from each site, after which a self-adhesive Ag/AgCl electrode† attached (active area 6.25 sq cm). Electrode impedances were typically below 500 Ω as measured with an impedance meter.‡ These sites were connected through a switching box to a Digitimer D180 stimulator§ for motor cortex stimulation. The stimulus

<table>
<thead>
<tr>
<th>Case Age (yrs) &amp; Sex</th>
<th>Surgical Procedure</th>
<th>Anesthetic Agents</th>
</tr>
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<tbody>
<tr>
<td>1 21, M</td>
<td>posterior wiring &amp; strut graft; anterior C5-6 &amp; C6-7 decompression &amp; fusion</td>
<td>N2O/narcotic</td>
</tr>
<tr>
<td>2 39, M</td>
<td>anterior C5-6 &amp; C6-7 decompression &amp; fusion</td>
<td>N2O/narcotic + enflurane (0.2%)</td>
</tr>
<tr>
<td>3 32, M</td>
<td>subarachnoid shunting of C-7 spinal cord cyst</td>
<td>N2O/narcotic</td>
</tr>
<tr>
<td>4 19, M</td>
<td>T-12 fracture decompression, T7-L3 Harrington rod instrumentation</td>
<td>N2O/narcotic + isoflurane (0.2%)</td>
</tr>
<tr>
<td>5 39, F</td>
<td>subarachnoid shunting of T-10 spinal cord cyst</td>
<td>N2O/narcotic</td>
</tr>
<tr>
<td>6 23, F</td>
<td>transoral decompression at C1-2</td>
<td>N2O/narcotic</td>
</tr>
<tr>
<td>7 23, F</td>
<td>posterior occiput-C-2 wiring</td>
<td>N2O/narcotic</td>
</tr>
<tr>
<td>8 45, M</td>
<td>T-10 fracture decompression with Harrington rod instrumentation</td>
<td>N2O/narcotic</td>
</tr>
</tbody>
</table>

* Stimulator manufactured by Grass Instrument Co., Quincy, Massachusetts.

† Ag/AgCl electrode supplied by Medtronic, Minneapolis, Minnesota.
‡ Impedance meter, Model EZM5A, manufactured by Grass Instrument Co., Quincy, Massachusetts.
§ Stimulator, Model D180, manufactured by Digitimer Ltd., Welwyn Garden City, England.

TABLE 1

Summary of patient data
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waveform approximated a decaying exponential with a time constant of 100 μsec. Stimulus intensities applied to our patients varied between 40% and 100% of the device output; in the D180 stimulator, these dial settings roughly correspond to between 300 and 750 V, with peak currents approaching 700 mA at maximum output. These charge densities are well within the recommended maximum safe levels. For comparison, it was found that in awake individuals stimulus magnitudes exceeding 40% on the Digitimer D180 output dial were always adequate to elicit upper-extremity MEP’s, and near-maximum muscle responses in the distal upper-extremity muscles were seen with magnitudes exceeding 60%. Those stimuli exceeding 60% in the present study should therefore be more than adequate for evoking motor responses under conditions where the patient was awake but resting. The EMG recordings were made with ½-in. platinum EEG-type needle electrode pairs positioned bilaterally within muscles appropriate to the nature of the surgery. For example, if the surgery involved the thoracolumbar spine and spinal cord, the majority of recording channels were devoted to the lower extremities. Eight muscles were typically instrumented among the deltoid, biceps brachii, extensor carpi radialis, flexor carpi radialis, abductor pollicis brevis, rectus femoris, tibialis anterior, medial gastrocnemius, and abductor hallucis muscle pairs. The EMG signals were amplified 30 Hz to 3 kHz (gain 1000 or 10,000), digitized, then stored on video-cassette tape.

Test Procedure

Once the patient had been anesthetized and positioned on the operating table, MEP testing was initiated. The thresholds for evoking motor activity with the anode at each of the C3*, C4*, and Cz* cortical sites were determined. Cortical stimuli were applied intermittently throughout the study at stimulus strengths between 40% and 100%. The minimum interval between successive stimuli was no less than 10 seconds, and between 80 and 200 individual cortical stimuli were delivered to each patient.

The effect of isoflurane on MEP responses was examined once closing of the surgical incision had begun. This period was chosen as it involves minimal risk of neurological insult to the patient, and hence is suitable for modifying anesthesia to the extent that MEP responses might be affected. A series of four stimulation trials using identical stimulus montage and magnitude was conducted, each trial separated by an interval of approximately 15 to 20 seconds. The vaporizer setting for the isoflurane was increased to 1.0% and maintained at that level for a period of 5 to 8 minutes, during which time cortical stimuli were applied once every 15 to 20 seconds. The maximum expired isoflurane concentration did not exceed 0.5 vol% in any patient during this time. Following this, the experimental portion of the study was effectively completed, and the anesthesiologist was free to alter the anesthetic regimen as appropriate. One of our requirements for this study was to minimize the additional time that each patient would remain under general anesthesia as a direct consequence of our experimental protocol; hence, we kept the period of isoflurane application brief. For this reason it is unlikely that the isoflurane concentration achieved a stable level in any patient within the relatively short period of application. Any effects of isoflurane observed for such a brief application would, by extension, be expected to be even more pronounced given a longer period to achieve equilibrium.

Data Analysis

An analysis of results, taken from the tape records, was carried out off-line. Data were played into a 16-channel analog-to-digital converter for computer analysis, using a sampling rate of 5 kHz for each channel. Signals were stored and analyzed utilizing a Dell System 310 PC-compatible computer and Computerscope EGAA hardware and software. Peak-to-peak amplitudes and latencies (measured at the takeoff point from baseline noise) of MEP’s were measured with digital cursors. Response amplitudes from the muscle demonstrating the largest EMG waveforms in each patient were used to investigate the effect of isoflurane. This approach was used since not all muscle groups gave consistent responses to cortical stimulation during acquisition of baseline responses; the stimulation montage used is optimal for either upper- or lower-extremity motor responses, but not for both simultaneously. The mean amplitude of four successive trials in each of three time periods (prior to turning on the isoflurane, and after 1 minute and 5 minutes of isoflurane application) was calculated and statistically analyzed with a repeated-measures multivariate analysis of variance (SPSS-X MANOVA, statistically significant at p < 0.05). Pair-wise comparisons of the three means were made with the Tukey (A) multiple-comparison method. Differences were considered to be statistically significant at p < 0.05.

Results

Each of the eight patients examined showed EMG responses in some or all of the monitored muscles following electrical noninvasive stimulation of the motor cortex during surgery. While the absolute magnitude of the responses sometimes varied considerably within the same patient at different stages of the study, this variability could be accounted for by differences in the extent of neuromuscular blockade in those patients receiving bolus injections of a relaxant agent. At no point during any procedure was there a change in EMG or SSEP responses which might have indicated com-

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promise of nerve tissue, and all patients awoke without evidence of further neurological deficit. No patient complained of ill-effects from the stimulation procedure.

Figure 1 illustrates EMG responses from various lower-extremity muscles in a patient who had sustained a T-12 vertebral burst fracture 20 days previously (Case 4). This patient was totally paraplegic initially; however, the paraplegia resolved over the next 72 hours to muscle weakness and patches of paresthesia in the right lower extremity. The spine was unstable, with several bone fragments impinging on the vertebral canal space. Decompression and corpectomy of T-12 was performed, and Harrington rods were applied from T-7 to L-3. Figure 1 shows EMG responses to cortical stimulation, between C2* (anode) and C3* (cathode), at 60% output during exposure of the fracture site. A clear response is seen in four of the six muscles, with latency increasing with the distance from the neuraxis. No EMG responses were obtained from the right tibialis anterior or abductor hallucis muscles at any time during the procedure, regardless of the combination of stimulus magnitude and montage used.

Figure 2 illustrates the effect of administration of isoflurane on EMG responses from a variety of upper-extremity muscles in one patient during stimulation between C4* and C2* at 40% output. In the responses obtained prior to adding isoflurane to the patient (Fig. 2 panel A), there is a similarity in MEP shape and latency for a given muscle from trial to trial. The results obtained with identical cortical stimuli delivered after 5 minutes of isoflurane inhalation (Fig. 2 panel B) showed that EMG responses from all muscle groups were attenuated, and nearly or completely absent for some muscles. After 5 minutes of isoflurane inhalation, to the extent that MEP responses were completely abolished in five of the eight patients at this time; these values are indicated by a column just exceeding the abscissa. A MANOVA examination of means (using absolute MEP amplitudes rather than transformed values) at each of the three study periods revealed a statistically significant difference (p < 0.05). Pair-wise comparisons of the individual means showed a statistically significant difference between the measurements before isoflurane and at 5 minutes after the start of isoflurane. Because of the problem of interference with cortical stimulation, we did not attempt to monitor SSEP responses during this brief period of isoflurane application. However, we have repeatedly seen that superimposition of relatively low levels of isoflurane onto pre-existing N2O/narcotic anesthesia, as done in this study, has little or no effect on SSEP responses (unpublished observations, see Discussion).

The neuromuscular blockade was discontinued 2 to 5 minutes before baseline measurements were obtained,

**FIG. 1.** Electromyographic discharges from various lower-extremity muscles in Case 4 in response to a single cortical stimulus at time 0. L = left; R = right; Rec. Fem. = rectus femoris; Tib. Ant. = tibialis anterior; Ab. Hal. = abductor hallucis. Vertical calibration bar = 500 µV for all traces except L. Ab. Hal. where bar = 200 µV.

**FIG. 2.** Muscle responses to four successive motor cortex stimuli before (panel A) and after (panel B) 5 minutes of administration of 1.0% isoflurane. Onset of each stimulus is indicated by the arrows at the top, thus each panel illustrates the responses to four successive stimuli. Stimuli are optimal for left upper-extremity responses, delivered between C4* (anode) and C2* at 40% output magnitude. Each response spans a 100-msec period and is separated from the next response by a stimulus artifact. Approximately 20 seconds elapsed between successive stimulus pulses. L = left; R = right; ECR = extensor carpi radialis.
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Fig. 3. Summary of motor evoked potential (MEP) amplitudes at different times before and after adding isoflurane to the anesthetic base. The muscle in each patient which gave the largest MEP's during the before-isoflurane trials was used for numeric analyses. The mean before-isoflurane value for each patient is transformed to a value of 1.0 to allow comparison between different patients; subsequent mean values are expressed as a fraction of this value for each patient. Values less than 1.0 thus indicate electromyographic attenuation. The value of the absolute mean MEP amplitude is shown in parentheses above each before-isoflurane column. The MEP responses were completely eliminated in five of the eight patients examined at the period of 8 minutes isoflurane. In these cases, a minimal response amplitude is indicated to aid in visualization.

contributing to the “Before Isoflurane” values (Fig. 3). If there was no interaction between isoflurane and the neuromuscular blockades given, we would have expected the level of neuromuscular blockade to decrease slowly during our period of repeated stimuli (but see Discussion). This tendency for decreased neuromuscular blockade (larger M-waves to direct peripheral nerve stimulation) in conjunction with greater attenuation of MEP's resulting from cortical stimulation (smaller muscle responses to cortical stimulation) is illustrated in Fig. 4. Following the addition of isoflurane, it is clear that the MEP response to cortical stimulation was effectively abolished while the M-wave amplitude rose slowly during the (approximately) 7 minutes of continued testing.

Figure 5 summarizes M-wave amplitude changes upon application of isoflurane. While muscle responses to peripheral nerve stimulation (M-waves) in the majority of patients tended to increase following administration of isoflurane, this effect was not statistically significant as determined by MANOVA of the means (using absolute M-wave amplitudes, rather than transformed values).

Discussion

The goal of this study was to develop a noninvasive and reliable method for activating descending central motor pathways during surgery. To be successful, we believe that the method should meet the following conditions: 1) it should not depend upon signal averaging, thereby providing immediate feedback about motor system function and integrity; 2) it should be
suitable for all levels of spine surgery; and 3) it should be easily managed without interference with other members of the surgical team. After preliminary trials using both electrical and electromagnetic stimulation of the motor cortex during surgery (and with extensive clinical experience with both procedures), we rejected the electromagnetic stimulator in favor of direct electrical stimulation. The Digitimer D180 electrical stimulator provides a stronger and more focal stimulation than present generations of electromagnetic coils are capable of producing. The electromagnetic coil is difficult to position accurately over the skull, particularly for surgical cases involving the cervical spine, and it overheats when driven repeatedly at high output. In fact, the only significant advantage to using the electromagnetic stimulator over the Digitimer D180 is the reduced discomfort of the patient; however, this becomes moot given the general anesthetics used during surgery.

Effects of Isoflurane

We found that noninvasive electrical stimulation of motor cortex resulted in reproducible MEP responses in all patients tested during surgery, provided that the inhalational anesthetic agent isoflurane was avoided or used at very low levels. The superimposition of as little as 0.4% isoflurane onto pre-existing N₂O/narcotic anesthesia led to dramatic attenuation or total elimination of EMG responses to motor cortex stimulation in all patients studied. The effect of isoflurane was especially noteworthy given that the degree of neuromuscular blockade was typically slowly declining during this testing period, a situation which would by itself normally lead to an increase in amplitude of the evoked motor responses. Furthermore, given the short duration of isoflurane administration, it is unlikely that any patient reached a plateau in uptake of isoflurane, such that the expired concentrations measured probably overestimate the actual delivery of isoflurane to the CNS.

The profound effect of low levels of isoflurane on EMG responses to cortical stimulation was unexpected. Isoflurane per se can act as a relatively weak skeletal muscle relaxant, and may also potentiate a pre-existing, nondepolarizing neuromuscular blockade. While this effect of isoflurane may account for the decrement in M-waves to peripheral nerve stimulation seen in Case 3 (Fig. 5), all other patients showed varying degrees of decline of neuromuscular blockade (that is, increasing M-waves) following addition of isoflurane to the anesthetic baseline. There is good agreement that isoflurane can cause suppression of spontaneous cortical activity in animals, as measured by EEG. Consistent with this are studies showing an attenuating action of isoflurane on cortical components of the SSEP in man. However, the concentrations of end-tidal isoflurane necessary to achieve EEG and/or SEP attenuation typically exceed 1.5 vol%, levels considerably greater than those demonstrated in this study to suppress CNS responsiveness to motor cortex stimulation.

This effect of low-level isoflurane on motor cortex output following stimulation is all the more surprising in light of the presumed mechanism of activation of the motor cortex by electrical transcranial cortical stimulation. Evidence suggests that this method causes direct depolarization at the initial segment of the upper motor neuron (or corticomotoneuron) axon, such that supraspinal synaptic activity is not a prerequisite for initiating MEPs. Conversely, signals giving rise to the SSEP must traverse a minimum of two supraspinal synapses, one at the dorsal column nuclei of the brain stem and one at the contralateral thalamus, prior to reaching the primary somatosensory cortex. Thus, fewer synapses are interposed along the pathway mediating EMG responses to cortical stimulation compared to that route for the SSEP, yet the former signals are more affected by increasing isoflurane concentration. Isoflurane may interfere with the initiation and conduction of action potentials within the corticomotoneurons mediating the MEP response, or it may suppress the spinal synapse between these cells and the α-motoneurons of the spinal cord. Isoflurane has been shown to exert a direct effect on transmembrane Ca⁺⁺-current in isolated ventricular myocytes, similar differential effects on Ca⁺⁺ conductance may occur in corticomotoneurons. We are currently investigating the site at which isoflurane interferes with MEP responses to motor cortex stimulation through peripheral reflex testing and direct spinal cord recordings of descending potentials caused by cortical stimulation.

Other Studies

Other reports of intraoperative motor stimulation have appeared in the literature. In a study conducted during surgery for scoliosis, the Digitimer D180 electrical stimulator was used for transcranial cortical stimulation to produce stable spinal cord potentials at recording sites caudal to the site of surgery in all patients studied. The anesthetic regimen included N₂O (70%), halothane (0.5%), and intermittent bolus injections of fentanyl and tubocurarine. No muscle responses were monitored in that study. In a different series, the Digitimer D180 stimulator was used to produce MEP's from thenar or anterior tibial muscles during spinal cord surgery. Those authors reported the attenuation or complete elimination of MEP's after adding N₂O to pre-existing narcotic anesthesia, whereas narcotic-based anesthetic regimens alone had little effect on MEP responsiveness. In light of the findings reported by Zentner, et al., it is possible that the effects of isoflurane demonstrated in the present study might have been potentiated by the pre-existing N₂O within the patient's system. While we are now investigating this possibility, our conclusion that isoflurane should be avoided during motor cortex stimulation remains unchanged.

Edmonds and coworkers reported on electromagnetic stimulation of motor cortex during spine surgery. Those authors found that 80% of patients undergoing scoliosis surgery demonstrated motor responses to mag-
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neural stimulation; the responses were characterized by large variability in amplitude and latency. Shields, et al.,26 found that the success rate for obtaining MEP’s in patients being operated on for disc herniation or spinal tumor was only 8%, causing these authors to conclude that electromagnetic stimulation might have “limited usefulness” for monitoring these types of neurosurgical patients. Our experience with the use of electromagnetic cortical stimulation to elicit MEP’s during surgery has also been one of limited success, although we have no difficulty in obtaining MEP’s with electromagnetic cortical stimulation in awake subjects (unpublished data).

Neuromuscular Blockade and MEP’s

One drawback to the procedure of monitoring muscle EMG as described in this report is the difficulty introduced by variations in neuromuscular blockade at different stages of the procedure. This problem can be adequately overcome through careful monitoring of muscle M-wave and twitch responses to supramaximal nerve stimulation, and by the use of a constant-infusion system for administering muscle relaxant.

Monitoring neuromuscular blockade at the soleus muscle appears to be particularly advantageous. The soleus muscle is normally activated both directly and indirectly (Hoffmann reflex) following appropriate stimulation of the tibial nerve at the popliteal fossa. The direct motor responses (M-wave) could be used to assess neuromuscular blockade in typical fashion. The reflex response (H-reflex), in which muscle afferents are electrically stimulated and monosynaptically excite α-motoneurons of the spinal cord, is roughly analogous to the tendon tap/segmental stretch reflex, and provides information about the excitability of spinal motoneurons. This information can help in our understanding of the sites and mechanisms of action of isoflurane and other central anesthetic agents.

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