Correlation between severity of clinical signs and motor evoked potentials after transcranial magnetic stimulation in large-breed dogs with cervical spinal cord disease

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Objective—To evaluate use of transcranial magnetic motor evoked potentials for assessment of the functional integrity of the cervical spinal cord in large-breed dogs with cervical spinal cord disease.

Design—Randomized, controlled, masked study.

Animals—10 healthy large-breed control dogs and 25 large-breed dogs with cervical spinal cord diseases.

Procedure—Affected dogs were allocated to 3 groups on the basis of neurologic status: signs of neck pain alone, ambulatory with ataxia in all limbs, or nonambulatory. Transcranial magnetic stimulation was performed on each dog with the same standard technique. Motor evoked potentials (MEP) were recorded from electrodes inserted in the tibialis cranialis muscle. Following the procedure, each dog was anesthetized and cervical radiography, CSF analysis, and cervical myelography were performed. The MEP latencies and amplitudes were correlated with neurologic status of the dogs after correction for neuronal path length.

Results—Mean MEP latencies and amplitudes were significantly different between control dogs and dogs in each of the 3 neurologic categories, but were not significantly different among dogs in the 3 neurologic categories. A linear association was evident between MEP latencies and amplitudes and severity of neurologic deficits; the more severe the neurologic deficits, the more prolonged the latencies and the more decreased the amplitudes.

Conclusions and Clinical Relevance—Transcranial magnetic MEP are useful to assess severity of cervical spinal cord disease in large-breed dogs. Impairment of the functional integrity of the cervical spinal cord was found even in dogs with neck pain alone. (*J Am Vet Med Assoc* 2002;221:60–64)

Stimuli applied to the scalp can excite the motor pathways, inducing muscle action potentials from fore- and hind limbs. A **motor evoked potential (MEP)** can be elicited with either a **transcranial electric stimulation (TES)** or a **transcranial magnetic stimulation (TMS)**.[1-3] In both, there is superficial stimulation of the motor cortex with resulting activation of the descending motor pathways (pyramidal and extrapyramidal systems).[4-8] An advantage of TMS over TES is that it is not painful and can be performed with or without sedation. **Transcranial magnetic MEP (TMMEP)** have been routinely used in human medicine to assess the functional integrity of the descending motor pathways in different types of spinal cord diseases, for intra-operative monitoring of the spinal cord, and as a prognostic tool in different neurologic disorders.[9-17] Transcranial magnetic stimulation has also been used in other neurologic conditions such as mood disorders (acting as an antidepressant), anxiety disorders, schizophrenia, movement disorders, and epilepsy.[18] In veterinary medicine, TMS has been performed on healthy animals to understand the behavior of TMMEP in different species and to standardize the method of stimulation.[19-25] Transcranial magnetic stimulation has also been used to assess anesthetic protocols to determine their impact on the recorded TMMEP.[26-31] In this regard, only 1 paper has been published on neurologically affected dogs.[32] In dogs with thoracolumbar intervertebral disc disease, a correlation existed between severity of the neurologic signs and MEP latencies and amplitudes. The purpose of the study reported here was to evaluate use of TMMEP for assessment of the functional integrity of the cervical spinal cord in large-breed dogs with cervical spinal cord diseases.

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Materials and Methods

Control dogs—Ten clinically normal large-breed dogs were obtained from the Animal Care Facility, University of Guelph. Complete physical and neurologic examinations were performed in all subjects. Physical examination included evaluation of temperature, pulse, and respiratory rates; general appearance of the subject; capillary refill time; and palpation of the peripheral lymph nodes. Neurologic examination included evaluation of the mental status, cranial nerves, gait and posture, postural reactions, spinal reflexes, and pain perception, as well as evaluation for back pain. Each dog was sedated with hydromorphone (0.1 mg/kg [0.04 mg/lb], IV) and acepromazine (0.03 mg/kg [0.01 mg/lb], IV). Because evaluation of muscle relaxation is subjective and anticipation of imminent stimulation was clearly perceived in certain dogs (with subsequent distortion of the waveforms), the sedation protocol was adjusted to effect for each dog. The depth of sedation was assessed subjectively on the basis of the degree of muscle relaxation, prolapse of the nictitating membrane, and mental tranquility of the dog, compared with these features assessed before sedation. After approximately 15 minutes, each dog was positioned in lateral recumbency

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and restrained by an animal health technician to ensure safety and cooperation. After 4 single TMS of the motor cortex and MEP recording from the tibialis cranialis muscle contralateral to the stimulated site, each dog was positioned on the other side to receive the same number of stimulations. The procedure lasted approximately 30 to 40 minutes. Each dog was then anesthetized with thiopental (10 mg/kg [4.5 mg/lb], IV), and anesthesia was maintained with isoflurane (1 to 2%). Diagnostic tests in all dogs included cervical spinal radiography, CSF collection from the cerebello-medullary cistern, and cervical myelography. Each dog was monitored by a technician throughout its recovery. The University of Guelph Animal Care Committee approved the study.

Dogs with spinal cord disease—Twenty-five large-breed dogs with a presumptive diagnosis of cervical spinal cord disease were studied. They were part of a research project studying TMMEP in Doberman Pinschers with cervical spondylopathy in relation to other large-breed dogs with any cervical spinal cord disease.[a] All dogs were evaluated upon referral to the Ontario Veterinary College by use of a complete physical and neurologic examination by the primary author (RP) and a faculty neurologist (JMP). The dogs were allocated to 3 categories on the basis of neurologic status: neck pain alone, ambulatory with ataxia in all limbs, and nonambulatory. Each dog had the same sedation protocol and diagnostic procedures as described for the control dogs.

Magnetic stimulation—The magnetic stimulation[b] was performed by the same person (RP). A focal-point coil, 9.5 cm in diameter, capable of producing a peak magnetic field of 2.2 Tesla at the coil surface was used. The maximum output of the stimulus intensity (100% stimulus; pulse width, 70 µs) was delivered by the magnetic coil held tangentially to the skull with the center of the coil over the motor cortex slightly lateral to the vertex. The coil was held in contact with the skin, and the current flow within the coil ran in a clockwise direction. Four individual stimulations were delivered 1 minute apart over the motor cortex of the stimulated site before repeating the procedure on the contralateral side. Therefore, a minimum of 8 stimuli were applied on each dog (4 repetitions × 2 sides).

Electromyography recording—Recordings were obtained by use of an electromyography unit.[c] Twelve-millimeter (0.5-in) disposable, noninsulated, surgical-grade stainless steel needles were used as the recording (active), reference, and ground electrodes.[d] The active electrode was inserted in the muscle belly of the tibialis cranialis muscle near the motor point, whereas the reference electrode was positioned subdermally approximately 1 cm distal to the active electrode. The ground electrode was placed subdermally between the stimulated site and the active electrode (ie, dorsal aspect of the cervical region). The recording electrode was connected to the negative input of the preamplifier (negative signal at recording electrodes causes upward deflection of the trace). The TMMEP were recorded from the right and left hind limbs while stimulating the contralateral cortex, respectively. The recorded MEP waveforms were saved and displayed on the oscilloscope screen. The low and high frequency filters were set at 30 Hz and 10 kHz, respectively; total recording time was 100 ms with a 10-ms delay to detect the onset of stimulus, and the sensitivity was set at 2000 µV/division. Four distinct waveforms were recorded from each muscle before stimulating the other side.

Measurement of latencies and amplitudes—The MEP latencies and amplitudes were calculated by use of manually directed cursors on the oscilloscope. Latencies were measured in milliseconds and were calculated as the interval from the onset of the stimulus and the onset of the response. Peak-to-peak amplitudes were measured in microvolts and were calculated from the peak of the negative-going wave to the nadir of the first positive-going wave (**Fig 1**).

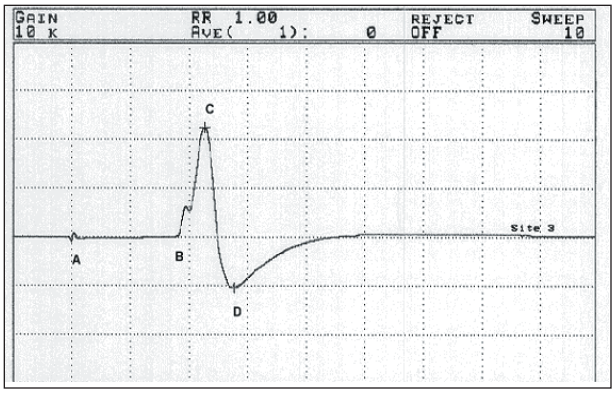

Figure 1—Electromyographic recording of a motor evoked potential (MEP) recorded after transcranial magnetic stimulation in a clinically normal dog. Latency was measured as the interval from the onset of stimulus (A) to the onset of the response (B). Peak-to-peak amplitude was calculated from the peak of the first negative wave (C) to the nadir of the first positive wave (D).

The neuronal path length of each dog was determined by use of a tape measure from the vertex to the active electrode located within the tibialis cranialis muscle contralateral to the stimulated site.

Statistical analyses—A 2-factor (side-group) ANCOVA for a mixed model with neuronal path length as the covariable was used to determine whether there were significant differences in latencies or amplitudes between dogs in each of the 3 neurologic categories and control dogs and among dogs in the 3 neurologic categories. An adjusted Tukey test was used for comparisons of multiple means. Multivariate regression analysis was performed with latency as the dependent variable and severity of neurologic signs and neuronal path length as independent continuous variables. The severity of neurologic signs was expressed with a score ranging from 0 to 3 (0 = normal, 1 = neck pain alone, 2 = ataxia in all limbs, 3 = nonambulatory). Statistical software was used for all analyses.[33] For all comparisons, a value of $P < 0.05$ was considered significant. The CSF results were not statistically analyzed, because there was no variability of the data (all dogs but 1 had CSF results within reference range).

Results

Control dogs—Nine mixed-breed dogs and 1 Golden Retriever were used; ages ranged from 6 months to 3.7 years (mean, 1.71 years). Five dogs were male and 5 were female, and weights ranged from 26.0 to 35.2 kg (57.3 to 77.6 lb), with a mean of 30.6 kg (67.3 lb). Neuronal path length ranged from 115 to 131 cm (mean, 118.3 cm; median, 117 cm) from the vertex to the active electrode located within the tibialis cranialis muscle contralateral to the stimulated site. The MEP recorded from the tibialis cranialis muscle was mainly biphasic or triphasic in shape, with onset latencies ranging from 17.1 to 20.9 ms and peak-to-peak amplitudes ranging from 1542.6 to 7358.3 µV (**Table 1**).

Dogs with spinal cord disease—Affected dogs included 11 Doberman Pinschers, 1 Nova Scotia Duck Tolling Retriever, 2 Great Danes, 1 Bernese Mountain

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Table 1—Mean ± SEM latency and amplitude of transcranial magnetic motor evoked potentials in control dogs (n = 10) and dogs with neck pain alone (category 1; 7), dogs that were ambulatory with ataxia in all limbs (category 2; 13), and dogs that were nonambulatory (category 3; 5)

Group	Latency (ms)	Amplitude (μV)
Control (n = 10)	18.8[a] ± 0.3	3752.3[c] ± 483.5
Category 1 (n = 7)	36.9[b] ± 7.2	1222.0[d] ± 269.1
Category 2 (n = 13)	44.7[b] ± 4.6	660.1[d] ± 143.6
Category 3 (n = 5)	51.8[b] ± 8.6	762.7[d] ± 336.7

[a-d]Within each column, values with different superscripts are significantly ($P \leq 0.05$) different.

Dog, 1 Golden Retriever, 4 Rottweilers, 1 Weimaraner, 1 Dalmatian, 1 Labrador Retriever, 1 Bouvier des Flandres, and 1 Bull Mastiff. The dogs were 2 to 11.5 years old (mean, 6.38 years); 15 dogs were male and 10 were female. The dogs' weight ranged from 25.0 to 60.0 kg (55.0 to 132.0 lb) with a mean of 41.69 kg (91.71 lb), and the neuronal path length ranged from 104 to 154 cm (mean 126.7 cm; median, 126.5 cm) from the vertex to the active electrode located within the tibialis cranialis muscle contralateral to the stimulated site.

On the basis of the neurologic examination and diagnostic procedures, the final diagnoses included cervical spondylopathy (n = 16), cervical disc disease (4), idiopathic signs of neck pain (no abnormal findings via diagnostic testing; 2), cervical intervertebral disc disease with concomitant cervical spondylopathy (1), and cervical spinal cord tumor (1). Onset of the clinical signs ranged from 1 week to 8 months before referral. All affected dogs had normal CSF results (WBC, $\leq 0.003 \times 10^9$/L), except for 1 dog with cervical spondylopathy (WBC, 0.008×10^9/L). This latter increase in cell count was attributed to inflammation secondary to cervical spondylopathy.

A significant difference was detected between mean MEP latencies and amplitudes of dogs in each of the 3 neurologic categories and those of the control dogs, but there were no significant differences in mean MEP latencies and amplitudes among dogs of the 3 neurologic categories (Table 1). There was a significant linear association (y = 11.35[x] + 9.87; where y is latency and x is degree of severity [from 0 to 3]) when mean MEP latencies and amplitudes of all dogs were correlated with severity of the neurologic deficits: the greater the neurologic deficits, the more prolonged the latencies and the more decreased the amplitudes **(Fig 2 and 3)**. When neuronal path length was analyzed as covariant, analysis revealed no influence of neuronal path length on the relationship between recorded latencies and severity of neurologic deficits.

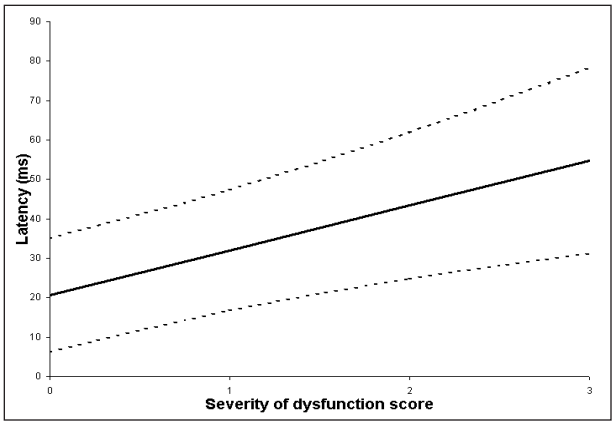

Figure 2—Linear regression analysis (solid line) of the relationship between onset latency of MEP recorded from the tibialis cranialis muscle contralateral to the site of transcranial magnetic stimulation and score for severity of cervical spinal cord dysfunction in 25 dogs. Dotted lines indicate 95% confidence intervals. Severity of dysfunction score: 0 = normal, 1 = neck pain alone; 2 = ataxia in all limbs; 3 = nonambulatory.

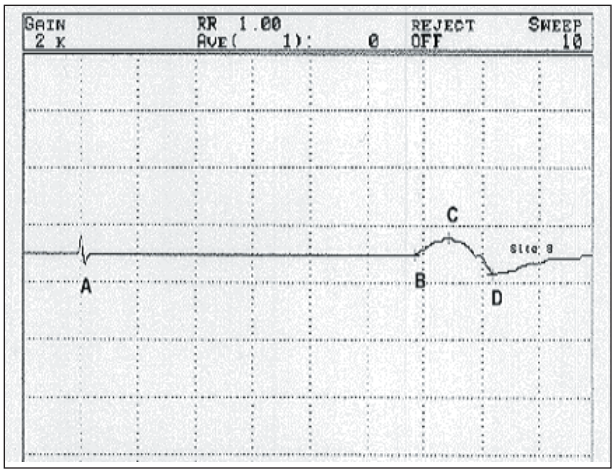

Figure 3—Electromyographic recording of an MEP recorded from the tibialis cranialis muscle after transcranial magnetic stimulation in a dog with cervical spinal cord disease. *See* Figure 1 for key. Notice latency is greater and amplitude is less than that of the clinically normal dog of Figure 1.

Discussion

The goal of this study was to evaluate efficacy of TMMEP in assessment of the functional integrity of the cervical spinal cord in healthy dogs and large-breed dogs with cervical spinal cord diseases, by correlating MEP latencies and amplitudes with severity of the neurologic signs. On the basis of our results, TMMEP revealed that spinal cord functional integrity is impaired in large-breed dogs with cervical spinal cord disease regardless of the severity of the neurologic abnormalities. This is in agreement with results reported in dogs with thoracolumbar disc disease in which a correlation between latencies and degree of severity was found.[32] Of special interest is the category of dogs with neck pain only and no other neurologic abnormality. In this category, cervical spinal cord lesions were confirmed by myelography in 5 of 7 dogs. Two dogs (a Bouvier des Flandres and a Mastiff) did not have myelographic abnormalities, but in all 7 dogs, MEP latencies and amplitudes were significantly abnormal, reflecting altered function of the cervical spinal cord. The results support the view that evidence of neck pain alone is not a benign clinical sign and that in certain dogs substantial spinal cord dysfunction is present. These findings are also in agreement with those of a study[34] of dogs with cervical intervertebral disc disease and signs of neck pain but without neurologic deficits in which 50 of 55 dogs had myelographic evidence of spinal cord compression.

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Results of our study also indicated that there were no significant differences in MEP latencies and amplitudes among dogs in the 3 neurologic categories. Despite this lack of a significant difference among groups, a linear association was observed when the mean latencies and amplitudes of all affected dogs were correlated with severity of neurologic deficits: the greater the neurologic deficits, the longer the latencies and the more decreased the amplitudes (Fig 2).

The tibialis cranialis muscle was used as the recording site. In a recent study,[a] we compared 2 groups of affected dogs (Doberman Pinschers with cervical spondylopathy and large-breed dogs of other breeds with spinal cord diseases, including cervical spondylopathy) with a control population via TMMEP. Of the 3 recording sites (eg, extensor carpi radialis and the flexor carpi ulnaris in forelimbs and tibialis cranialis in the hind limbs), the tibialis cranialis muscle provided the most reliable results, and a significant difference from the control group was observed in mean latencies when the tibialis cranialis muscle was used to record TMMEP in all abnormal dogs.[a]

A morphologic variation of the MEP waveforms was occasionally recorded in the present study. Variability of waveforms is reported to be influenced by stimulus intensity, coil size, mental alertness, and prestimulus muscle contraction.[35]

Cervical spondylopathy (or wobbler syndrome) frequently affects Doberman Pinschers and other large-breed dogs. It is believed that most Doberman Pinschers have abnormal congenital cervical vertebral conformation that makes them highly predisposed to develop the disease at > 5 years of age.[36] In our study, the significant difference observed in MEP latencies and amplitudes between dogs with signs of neck pain and the control dogs may warrant further investigation of Doberman Pinschers. Two of the 7 dogs in this category were Doberman Pinschers with spinal cord compression that was confirmed myelographically. Clinical signs of neck pain are often absent in Doberman Pinschers with cervical spondylopathy, and clinically normal Doberman Pinschers may have subclinical cervical spinal cord abnormalities if prolonged latencies and decreased amplitudes are detected. If this hypothesis is proven, TMMEP have the potential to become a useful screening tool for cervical spondylopathy in this breed.

[a]Poma R. The use of transcranial magnetic stimulation in the evaluation of Doberman Pinschers with cervical spondylopathy. DVSc thesis, Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, ON, Cananda, 2001.

[b]Cadwell model MES-10, serial No. MS0200364, Cadwell Laboratories Inc, Kennewick, Wash.

[c]Cadwell model Excel, serial No. 081290175, Cadwell Laboratories Inc, Kennewick, Wash.

[d]Cadwell Laboratories Inc, Kennewick, Wash.

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