Disk-associated wobbler syndrome is one of a collection of disorders affecting the caudal cervical vertebrae and intervertebral disks of large breed dogs and is the most common underlying disorder in dogs with wobbler syndrome (cervical spondylomyelopathy). Caudal cervical spinal cord compression is typically caused by protrusion of 1 or more intervertebral disks, sometimes in combination with dorsal compression resulting from hypertrophy of the ligamentum flavum and mild vertebral body malformations. Although DAWS can affect several breeds of large breed dogs, Doberman Pinschers are overrepresented. The most common clinical appearance is a gait disturbance with ataxia, paresis, or both affecting the pelvic limbs, frequently in combination with a short, stilted gait in the thoracic limbs. This disorder can be diagnosed by a variety of imaging modalities, such as myelography, computed tomography-myelography, and MRI. Each of these techniques is associated with spe-
cific advantages and disadvantages. During the past decade, MRI has gained popularity and several previous reports have described its use to characterize a variety of neurologic disorders affecting the cervical vertebral column and spinal cord in dogs. Magnetic resonance imaging allows direct, noninvasive, multiplanar imaging and excellent soft tissue characterization with an absence of ionizing radiation. A disadvantage of MRI for evaluation of the vertebral column and spinal cord is the possibility of clinical overinterpretation. Several studies, involving human and veterinary patients, have demonstrated the occurrence of cervical spinal cord compression on magnetic resonance images from clinically normal subjects. A recent study comparing results of low-field MRI in Doberman Pinschers with DAWS found that low-field MRI of the cervical vertebral column and spinal cord could lead to false-positive and false-negative assessments of suspected clinical status. In that study, 2 of 21 clinically affected dogs were erroneously categorized, on the basis of MRI findings alone, as clinically normal and 4 of 23 clinically normal dogs were categorized as clinically affected.

Transcranial magnetic stimulation is a noninvasive, painless, and sensitive technique for stimulating the cerebral cortex. It may be used to evaluate the functional integrity and conduction speed of the fastest conducting descending motor pathways in the brain and spinal cord. Magnetic motor cortex stimulation evokes synchronized descending excitatory volleys in the spinal cord pathways. These excitatory volleys induce muscle twitches that are recorded as potentials in the periphery. These potentials are called TMMEPs. In human medicine, TMS has been widely used to assess the integrity of the spinal cord in patients with various spinal cord disorders, for intraoperative monitoring, and as a prognostic tool. In veterinary medicine, it has been performed in healthy dogs and horses, to standardize the method of stimulation and to assess the effect of various anesthetic protocols on recorded TMMEPs. This technique has also been used in horses with bilateral hind limb ataxia and cervical spinal cord lesions and in dogs with thoracolumbar intervertebral disk disease, cervical spinal cord disease, and cervical spondylomyelopathy.

The purpose of the study reported here was to evaluate the use of TMS for differentiating between clinically relevant and clinically irrelevant spinal cord compression evident on magnetic resonance images of dogs with and without DAWS. Because TMS provides objective information on spinal cord function, we hypothesized that this technique could be used to differentiate between clinically relevant and clinically irrelevant spinal cord compression as seen on MRI. Additionally, we wanted to compare our results with previously established reference values for TMMEPs in clinically normal Doberman Pinschers and assess whether there was a correlation between TMS and a published MRI compression scale.

Materials and Methods

Animals—Thirty-three client-owned Doberman Pinschers were included in the study. The study was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment.

Three groups of dogs were studied. The first group consisted of 11 clinically normal Doberman Pinschers without MRI evidence of spinal cord compression. This group included 6 males and 5 females between 1.5 and 8 years old (mean, 4.3 years; median, 4.5 years). The second group consisted of 6 clinically normal Doberman Pinschers with MRI evidence of spinal cord compression. This group included 3 males and 3 females between 1.6 and 7.1 years old (mean, 4.0 years; median, 3.9 years). The third group consisted of 16 Doberman Pinschers with MRI evidence of spinal cord compression and clinical signs of DAWS. This group included 6 males and 10 females between 4.6 and 10 years old (mean, 8.6 years; median, 8.7 years). Clinical signs in these dogs ranged from cervical hyperesthesia only (n = 2) to ambulatory paraparesis, ataxia, or both with or without cervical hyperesthesia (5); ambulatory tetraparesis, ataxia, or both with or without cervical hyperesthesia (7); and nonambulatory tetraparesis with or without cervical hyperesthesia (2).

All dogs underwent complete physical and neurologic examinations at the time of enrollment in the study. In addition, a CBC, serum biochemical analysis, echocardiographic examination, and standardized measurement of mucusosal bleeding time were performed. All clinically normal Doberman Pinschers underwent follow-up physical and neurologic examinations between 16 and 18 months after the initial evaluation to determine whether any recorded MRI or TMS abnormalities could be regarded as truly clinically unimportant or rather as indicative of early onset of disease prior to development of clinical signs. Neurologic examinations of all dogs were performed by a single individual (SDD).

TMS—Motor cortex magnetic stimulation was performed by use of a commercially available magnetic stimulator with a circular coil 45 mm in external diameter that generated a peak magnetic field of approximately 4 T. Maximal (ie, 110%) stimulator output was used to ensure identifiable TMMEPs. The magnetic coil was placed tangentially to the skull and in contact with the skin, with the center of the coil placed over the vertex (Figure 1).
Recording of TMMEPs—Recordings were obtained by use of an electromyography unit. Magnetic motor evoked potentials were recorded successively from the left thoracic, right thoracic, left pelvic, and right pelvic limbs with monopolar needle electrodes inserted in the muscle belly of the ECRM in the thoracic limbs and the CTM in the pelvic limbs. The tip of the recording electrode was positioned in the middle of the muscle belly, just cranial to the lateral humeral epicondyle for the ECRM and slightly lateral to the distal end of the tibial crest for the CTM. The reference electrode was a subdermal needle electrode positioned subcutaneously over tendons at the level of the carpal and the tarsal joints for the ECRM and the CTM, respectively. The ground electrode was placed subcutaneously over the olecranon of the thoracic limb or over the patella of the pelvic limb. The low- and high-frequency filters were set at 20 Hz and 10 kHz, respectively. Sensitivity was set at 10 mV/division but was increased if the peak-to-peak amplitude was low. Analysis time was 100 milliseconds following the stimulus.

Measurements of the TMMEP onset latency and peak-to-peak amplitude were made manually by use of the cursors on the oscilloscope. Onset latency was measured as the shortest time between the trigger point and the cursors on the oscilloscope. Onset latency was measured between the 2 largest peaks of opposite polarity. Individual stimulations were delivered until 2 reproducible TMMEPs were recorded. Magnetic motor evoked responses were considered absent if 4 consecutive stimulations consistently failed to elicit a reproducible TMMEP. In dogs with absent TMMEPs, onset latency was regarded as infinite and peak-to-peak amplitude was recorded as 0 mV. The neuronal path length of each dog was measured from the vertex to the contralateral active electrode located within the ECRM or CTM with a tape measure placed on the surface of the skin.

MRI—A permanent 0.2-T magnet was used to perform MRI in all dogs, as described. Dogs were anesthetized, and T1- and T2-weighted spin echo and T2-weighted fast spin echo studies were performed in all dogs in the sagittal (C2 to C7), dorsal (C2 to C7), and transverse (C4 to C7) planes. Slice thickness was 4 mm in the sagittal and dorsal images and 3 mm in the transverse images with no interslice gap.

Magnetic resonance images were examined for evidence of spinal cord compression, defined as complete subarachnoid space compression with deviation or distortion of the spinal cord. In dogs with spinal cord compression, the severity of compression was scored on a scale from 0 to 3 at the level of the spinal cord that was most severely affected. Scores were assigned on the basis of degree of spinal cord deformation and displacement and severity of ISI changes, as described. Grade 0 indicated no evidence of cord compression, grade 1 indicated mild indentation of the spinal cord with a dorsoventral cord diameter that was not less than two-thirds of the expected cord diameter, grade 2 indicated notable spinal cord indentation with a dorsoventral cord diameter that was less than two-thirds of the expected cord diameter but not associated with ISI changes within the cord, and grade 3 indicated notable spinal cord indentation associated with ISI changes. The expected spinal cord diameter was defined as the cord diameter adjacent to the site of spinal cord compression. Changes in ISI were evaluated on the basis of relative increase in signal on T2-weighted images, decrease in signal on T1-weighted images, or both, compared with the surrounding spinal cord parenchyma.

Data analysis—For all TMMEP variables (ie, onset latency, peak-to-peak amplitude, and neuronal path length for the ECRM and for the CTM), values recorded in each dog for the left and right limbs were averaged to obtain a single value for each variable for the ECRM and the CTM for each dog. Statistical analyses were performed on the basis of nonparametric, rank-based methods with a commercial software package. Nonparametric methods were used because the data could not be assumed to be normally distributed and because no values for onset latency were obtained in some instances, and a value of infinity was assumed.

Kruskall-Wallis 1-way ANOVA was used to compare values for onset latency and peak-to-peak amplitude among the 3 clinical groups, with values of P < 0.05 considered significant. Pairwise comparisons were performed with the 2-sided Wilcoxon rank sum test. Because of the multiple comparisons, a Bonferroni adjustment was made to the cutoff for significance, with values of P < 0.017 considered significant. Kendall correlation coefficients were calculated between onset latency and neuronal path length and between spinal compression score and onset latency and peak-to-peak amplitude. The signed rank test was used to compare values for onset latency and peak-to-peak amplitude recorded from the left and right limbs, with values of P < 0.05 considered significant.

Receiver operator characteristic curves (calculated with a commercial software program) were created for use of ECRM and CTM onset latencies and peak-to-peak amplitudes to distinguish between clinically normal Doberman Pinschers and Doberman Pinschers with DAWs. In general, ROC curves can be used to identify the optimal cutoff between normal and abnormal values for diagnostic tests, with each value on an ROC curve representing a tradeoff between sensitivity (ability to detect an affected dog) and specificity (ability to detect an unaffected dog). Tests that combine high sensitivity with high specificity are best at discriminating between affected and unaffected dogs. The area under an ROC curve quantifies the overall ability of the
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A useless test (no discrimination) will have an area under the curve of 0.5; a perfect test will have an area under the curve of 1.0.

Results

Table 1—Median onset latencies, peak-to-peak amplitudes, and neuronal path lengths for TMMEPs recorded from the ECRM and CTM in clinically normal Doberman Pinschers without (group 1; n = 11) and with (group 2; 6) spinal cord compression on MRI and 16 Doberman Pinschers with DAWs (group 3).

<table>
<thead>
<tr>
<th>Group</th>
<th>Onset latency (ms)</th>
<th>Peak-to-peak amplitude (mV)</th>
<th>Neuronal path length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ECRM: 13.75 (12.25–16.95)</td>
<td>7.52 (1.86–19.45)</td>
<td>74.75 (63.0–82.0)</td>
</tr>
<tr>
<td></td>
<td>CTM: 21.75 (18.65–37.1)</td>
<td>5.52 (0.81–12.50)</td>
<td>125.0 (111.0–130.0)</td>
</tr>
<tr>
<td>2</td>
<td>ECRM: 13.62 (12.75–15.90)</td>
<td>6.00 (2.66–15.72)</td>
<td>71.5 (67.0–75.0)</td>
</tr>
<tr>
<td></td>
<td>CTM: 20.9 (19.55–28.6)</td>
<td>7.50 (0.42–16.70)</td>
<td>121.5 (112.0–135.5)</td>
</tr>
<tr>
<td>3</td>
<td>ECRM: 17.72 (13.25–26.4)</td>
<td>4.06 (0.098–11.98)</td>
<td>79 (68.0–86.0)</td>
</tr>
<tr>
<td></td>
<td>CTM: ∞ (∞–31.7) *</td>
<td>0* (0–2.74)</td>
<td>123.0 (96.5–150.0)</td>
</tr>
</tbody>
</table>

Data are reported as median (range).

*In 2 of the 16 clinically affected Doberman Pinschers, TMMEPs could be elicited in both pelvic limbs, and in 3, TMMEPs could be elicited in 1 pelvic limb. No response was recorded in the remaining 11 dogs. Onset latency was regarded as infinite and peak-to-peak amplitude was recorded as 0 mV if TMMEPs were absent.

Figure 2—Sagittal (A) and transverse (B; image obtained at the level of C6-7) T2-weighted magnetic resonance images of a 5-year-old clinically normal Doberman Pinscher and magnetic motor evoked potentials recorded from the left ECRM (C; upper trace) and left CTM (lower trace). The arrow indicates the stimulus artifact. Vertical bars indicate onset latency, and horizontal bars indicate peak-to-peak amplitude.

Figure 3—Sagittal (A) and transverse (B; image obtained at the level of C6-7) T2-weighted magnetic resonance images of a 6-year-old Doberman Pinscher with ambulatory paraparesis, ataxia, and cervical hyperesthesia attributed to DAWs and magnetic motor evoked potentials recorded from the left ECRM (C; upper trace) and left CTM (lower trace). Ventral and dorsal spinal cord compression at C5-6 and C6-7 is evident, along with an increase in ISI at C5-6. Notice that both potentials are polyphasic; onset latencies are prolonged, and peak-to-peak amplitudes are decreased. Sensitivity was increased to 5 mV/division to allow visualization of the TMMEP and measurement of onset latency and peak-to-peak amplitude.

Figure 4—Sagittal (A) and transverse (B; image obtained at the level of C5-6) T2-weighted magnetic resonance images of a 6-year-old Doberman Pinscher with ambulatory paraparesis, ataxia, and cervical hyperesthesia attributed to DAWs and magnetic motor evoked potentials recorded from the left ECRM (C; upper trace) and left CTM (lower trace). Ventral and dorsal spinal cord compression at C5-6 and C6-7 is evident, along with an increase in ISI at C5-6. Notice that both potentials are polyphasic; onset latencies are prolonged, and peak-to-peak amplitudes are decreased. Sensitivity was increased to 5 mV/division to allow visualization of the TMMEP and measurement of onset latency and peak-to-peak amplitude.

Results

Median values and ranges for onset latency, peak-to-peak amplitude, and neuronal path length for the 3 groups of Doberman Pinschers were calculated (Table 1) from recorded TMMEPs. In 11 of the 16 Doberman Pinschers with clinical signs of DAWs, TMMEPs could not be recorded in either pelvic limb. In an additional 3, TMMEPs could be recorded in only 1 pelvic limb, and in the 2 remaining, TMMEPs could be recorded in both pelvic limbs. Waveforms of TMMEPs recorded from the ECRM and CTM were mainly biphasic or triphasic in the clinically normal dogs and mainly polyphasic in the clinically affected dogs (Figures 2–4).
For both the ECRM and the CTM, onset latencies for clinically affected Doberman Pinschers were significantly different from values for both of the 2 groups of clinically normal dogs (Table 2), but there were no significant differences in ECRM or CTM onset latencies between the 2 groups of clinically normal dogs. There were no significant differences for ECRM peak-to-peak amplitude among the 3 groups. However, CTM peak-to-peak amplitudes for clinically affected Doberman Pinschers were significantly different from values for both of the 2 groups of clinically normal dogs. There was no significant difference in CTM peak-to-peak amplitudes between the 2 groups of clinically normal dogs.

Threshold values for ECRM and CTM onset latencies and CTM peak-to-peak amplitudes were identified from the ROC curves. A value of 16 milliseconds for ECRM onset latency corresponded to a sensitivity of 0.75 and specificity of 0.9 when used to discriminate between clinically normal and clinically affected dogs (Figure 5). A value of 32 milliseconds for CTM onset latency corresponded to a sensitivity of approximately 0.9 and specificity of approximately 0.9.

Table 2—Results of comparison of onset latencies and peak-to-peak amplitudes for TMMEPs recorded from the ECRM and CTM in the 3 groups of dogs in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Group 1 vs 2</th>
<th>Group 1 vs 3</th>
<th>Group 2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset latency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECRM</td>
<td>&lt; 0.001</td>
<td>0.80</td>
<td>0.003</td>
<td>0.009</td>
</tr>
<tr>
<td>CTM</td>
<td>&lt; 0.001</td>
<td>0.40</td>
<td>&lt; 0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak-to-peak amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECRM</td>
<td>0.22</td>
<td>0.66</td>
<td>0.10</td>
<td>0.37</td>
</tr>
<tr>
<td>CTM</td>
<td>&lt; 0.001</td>
<td>0.98</td>
<td>&lt; 0.001</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data represent P values. Because of the multiple comparisons, values of P < 0.017 were considered significant.

Figure 5—Receiver operator characteristic curve for ECRM onset latency in 16 Doberman Pinschers with DAWS and 17 clinically normal Doberman Pinschers. An onset latency of 13 milliseconds corresponded to a sensitivity of 1.0, and an onset latency of 18 milliseconds corresponded to a specificity of 1.0. None of the clinically affected dogs had an ECRM onset latency < 13 milliseconds, and none of the clinically normal dogs had an ECRM onset latency > 18 milliseconds. A cutoff value of 16 milliseconds corresponded to a sensitivity of 0.75 and specificity of 0.9.

Figure 6—Receiver operator characteristic curve for CTM onset latency in 16 Doberman Pinschers with DAWS and 17 clinically normal Doberman Pinschers. A cutoff value of 32 milliseconds corresponded to a sensitivity of approximately 0.9 and specificity of approximately 0.9.
None of the 3 groups had significant differences in onset latencies or peak-to-peak amplitudes between the left and right limbs. When all dogs were considered as a single group, the only significant correlation between onset latency and neuronal path length that was identified was between ECRM onset latency and neuronal path length for the right thoracic limb ($r = 0.26; P = 0.043$).

All 11 clinically normal Doberman Pinschers without MRI evidence of spinal cord compression had grade 0 spinal cord compression. Of the 6 clinically normal Doberman Pinschers with MRI evidence of spinal cord compression, 5 had grade 1 spinal cord compression and 1 had grade 2 spinal cord compression. Of the 16 Doberman Pinschers with DAWS, 5 had grade 1 spinal cord compression, 2 had grade 2 spinal cord compression, and 9 had grade 3 spinal cord compression. There were significant correlations between spinal cord compression score and ECRM onset latency ($r = 0.42; P = 0.002$), CTM onset latency ($r = 0.41; P = 0.003$), and CTM peak-to-peak amplitude ($r = -0.41; P = 0.003$).

Of the 17 clinically normal Doberman Pinschers, 15 were available for complete physical and neurologic examinations between 16 and 18 months after the MRI and TMS examinations. These examinations revealed no abnormalities. The 2 remaining dogs were euthanized for reasons unrelated to this study. According to the owners, they never demonstrated signs suggestive of cervical hyperesthesia or cervical myelopathy.

**Discussion**

In the present study, there were significant differences in ECRM and CTM onset latencies between the Doberman Pinschers with DAWS and 2 groups of clinically normal dogs. In addition, there were significant correlations between severity of spinal cord compression and ECRM onset latency, CTM onset latency, and CTM peak-to-peak amplitude. These results suggest that TMS can be used as a diagnostic tool to differentiate between clinically relevant and clinically irrelevant cervical spinal cord compression in dogs.

Previous studies have demonstrated the application of TMS as a valuable diagnostic tool in dogs with cervical spondylomyelopathy and other spinal cord disorders. However, data on TMS findings in dogs with clinically irrelevant spinal cord compression are scarce. Median values for clinically normal Doberman Pinschers for both ECRM and CTM onset latency in the present study were comparable with mean values reported by da Costa et al.

In the present study, values for onset latency were particularly useful to differentiate between clinically relevant and clinically irrelevant spinal cord compressions seen on magnetic resonance images, and values for peak-to-peak amplitude were less useful for this purpose. Recorded peak-to-peak amplitudes were also associated with large differences between minimum and maximum values, and values obtained in the present study were different from reported reference values for clinically normal Doberman Pinschers. Therefore, in agreement with results of earlier studies, values for peak-to-peak amplitude may be assumed to be of limited clinical value. Peak-to-peak amplitude is influenced by the number of fibers recruited by the stimulus, the number of motor neurons excited by the descending impulses, the characteristics of the target muscle, and alterations in the position of the magnetic stimulating coil over the surface of the cranium. The variability in these factors appears to be spontaneous, and its cause is unknown.

When compared with the threshold values obtained from the ROC curves, 2 clinically normal dogs without MRI evidence of spinal cord compression in the pres-
In the present study, there was a significant correlation between severity of spinal cord compression on magnetic resonance images, as determined with a published scale, and the onset latencies for ECRM and CTM and the peak-to-peak amplitude for CTM. Our results confirmed those obtained by da Costa et al. in a study of Doberman Pinschers with cervical spondylomyelopathy and can probably at least in part be explained by our finding of a grade 3 spinal cord compression only in clinically affected dogs. Therefore, further studies are warranted to investigate whether this result truly suggests that TMS findings correlate with degree of spinal cord compression seen on MRI or only illustrates the difference between rather severe clinically relevant and rather minor clinically irrelevant spinal cord compression.

The present study was limited by the small number of dogs that were included. This was especially true for the clinically normal dogs with MRI evidence of spinal cord compression. This hampered the formulation of reliable reference ranges for onset latency and peak-to-peak amplitude values for the various groups of Doberman Pinschers. For this reason, ROC curves were constructed to identify threshold values for the measured variables. Our findings should encourage further exploration of the use of TMS in veterinary medicine for the assessment of spinal cord disorders in various breeds of dogs.

References