Comparison of magnetic and electrical phrenic nerve stimulation in assessment of phrenic nerve conduction time

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Similowski, Thomas, Selma Mehirí, Alexandre Duguet, Valérie Attali, Christian Straus, and Jean-Philippe Derenne. Comparison of magnetic and electrical phrenic nerve stimulation in assessment of phrenic nerve conduction time. J. Appl. Physiol. 82(4): 1190–1199, 1997.—Cervical magnetic stimulation (CMS), a nonvolitional test of diaphragm function, is an easy means for measuring the latency of the diaphragm motor response to phrenic nerve stimulation, namely, phrenic nerve conduction time (PNCT). In this application, CMS has some practical advantages over electrical stimulation of the phrenic nerve in the neck (ES). Although normal ES-PNCTs have been consistently reported between 7 and 8 ms, data are less homogeneous for CMS-PNCTs, with some reports suggesting lower values. This study systematically compares ES- and CMS-PNCTs for the same subjects. Surface recordings of diaphragmatic electromyographic activity were obtained for seven healthy volunteers during ES and CMS of varying intensities. On average, ES-PNCTs amounted to 6.41 ± 0.84 ms and were little influenced by stimulation intensity. With CMS, PNCTs were significantly lower (average difference 1.05 ms), showing a marked increase as CMS intensity lessened. ES and CMS values became comparable for a CMS intensity 65% of the maximal possible intensity of 2.5 Tesla. These findings may be the result of phrenic nerve depolarization occurring more distally than expected with CMS, which may have clinical implications regarding the diagnosis and follow-up of phrenic nerve lesions.

Diaphragm; cervical magnetic stimulation; phrenic latency

CERVICAL MAGNETIC STIMULATION (CMS) provokes contraction of several muscle groups innervated by cervical roots (4, 26), including the diaphragm (30). When combined with measurements of transdiaphragmatic pressure (Pdi) (30, 32) or of mouth pressure (10), it provides an easy-to-use, noninvasive, and nonvolitional test of diaphragm contractile properties and of diaphragm degree of activation (29). It can be an especially powerful tool to study the electromyographic (EMG) response of the diaphragm to phrenic nerve stimulation in combination with surface or esophageal recordings of diaphragmatic activity. Indeed, it may well have several advantages over transcutaneous or needle electrical stimulation of the phrenic nerve (ES). The phrenic nerve can be difficult to find through ES; the absence of a clear diaphragmatic EMG response with this technique may only result from the operator’s inability to locate the nerve (thus yielding a false negative). A similar false-negative reading is much less likely to occur with CMS; medium-sized circular coils generally used produce widespread magnetic fields. Thus absence of diaphragmatic EMG response to CMS is much more likely to be the result of actual phrenic nerve dysfunction than to failure of the stimulus to reach the nerve. In addition, the right and the left phrenic nerves can be studied simultaneously, with a single stimulus. Furthermore, CMS is generally painless (or almost so) and thus is well accepted by most patients. This is not always the case with conventional ES because of both current intensities and the frequent need for the operator to impose a significant pressure on the soft tissues of the neck to optimize the stimulation.

Nevertheless, CMS and ES have different mechanisms and sites of action. Despite the fact that both techniques may provide equivalent results, it is important to evaluate those results before recommending CMS for phrenic nerve conduction studies.

Methods

Subjects

Seven healthy volunteers (5 men and 2 women; all between 21 and 35 yr of age) participated in the study (Table 2) after approval by the local ethical committee. All subjects were studied while they were sitting on a chair equipped with headrests, abdomen unbound. They had been informed of the purpose of the study and methods used.

EMG. Surface recordings of the right and left costal diaphragmatic EMG activity were obtained by using dispos-
of phrenic nerve and of cervical magnetic stimulation at maximal output of the stimulator

Table 1. Summary of results of 9 representative studies over 30 years of phrenic nerve conduction time by using transcutaneous electrical stimulation

<table>
<thead>
<tr>
<th>Author, Year, Ref. No.</th>
<th>No. of Subjects</th>
<th>PNCT, ms</th>
<th>R-PNCT, ms</th>
<th>L-PNCT, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delhez, 1965 (8)</td>
<td>30</td>
<td>7.70 ± 0.80</td>
<td>7.50 ± 0.53</td>
<td>8.2 ± 0.71</td>
</tr>
<tr>
<td>Newcom-Davis, 1967 (23)</td>
<td>18</td>
<td>8.40 ± 0.78</td>
<td>7.50 ± 0.53</td>
<td>8.20 ± 0.71</td>
</tr>
<tr>
<td>Delhez, 1979 (7)</td>
<td>30</td>
<td>7.44 ± 0.59</td>
<td>(R-to-L ≠ 0.08 ± 0.42)</td>
<td></td>
</tr>
<tr>
<td>Shaw et al., 1980 (28)</td>
<td>60</td>
<td>7.00 ± 0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maclean and Mattioni, 1981 (17)</td>
<td>30</td>
<td>7.68 ± 0.56</td>
<td>7.92 ± 0.92</td>
<td></td>
</tr>
<tr>
<td>DelTroyer and Vanderhoeft, 1982 (6)</td>
<td>31</td>
<td>6.94 ± 0.77</td>
<td>6.61 ± 0.77</td>
<td></td>
</tr>
<tr>
<td>McKenzie and Gandevia, 1985 (19)</td>
<td>20</td>
<td>6.54 ± 0.77</td>
<td>(R-to-L ≠ 0.34 ± 0.27)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. PNCT, phrenic nerve conduction time; R-PNCT, right phrenic nerve conduction time; L-PNCT, left phrenic nerve conduction time; R-to-L ≠, right-to-left difference between PNCTs. 1Recordings were made from an esophageal electrode; esophageal diaphragm muscle only; 2minimal value 6.1 ms, age 20–61, no correlation between PNCT and age; 3control group in a study of phrenic nerve function after pneumonectomy; 4PNCT to cranial fibers of diaphragm averaged 6.82 ± 0.64 ms on right and 7.93 ± 0.85 ms on left; significant correlations between PNCT and age and height of subjects; 5PNCT was measured in 110 individuals, including 84 normal subjects, aged 21–89 yr; correlation between PNCT and age or height was weak; 6positive correlation between PNCT and age; minimal reported value 5.5 ms (shortest PNCT in 9 studies).

Table 2. Characteristics of subjects and results of supramaximal electrical transcutaneous stimulation of phrenic nerve and of cervical magnetic stimulation at maximal output of the stimulator

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>ES-PNCT</th>
<th>CMS-PNCT (I_{max}, CW, ms)</th>
<th>CMS-PNCT (I_{max}, CCW, ms)</th>
<th>CMS-PNCT (Threshold, CW, ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>28</td>
<td>175</td>
<td>70</td>
<td>7.51</td>
<td>5.28</td>
<td>5.35</td>
<td>5.45</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>31</td>
<td>164</td>
<td>54</td>
<td>8.62</td>
<td>5.66</td>
<td>5.50</td>
<td>5.18</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>33</td>
<td>162</td>
<td>55</td>
<td>6.44</td>
<td>4.86</td>
<td>4.43</td>
<td>4.82</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>35</td>
<td>187</td>
<td>98</td>
<td>5.94</td>
<td>6.62</td>
<td>5.54</td>
<td>9.88</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>21</td>
<td>179</td>
<td>73</td>
<td>6.98</td>
<td>5.66</td>
<td>5.63</td>
<td>6.80</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>25</td>
<td>172</td>
<td>64</td>
<td>6.28</td>
<td>4.94</td>
<td>5.28</td>
<td>7.25</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>25</td>
<td>170</td>
<td>67</td>
<td>5.00</td>
<td>5.18</td>
<td>5.05</td>
<td>6.36</td>
</tr>
</tbody>
</table>

Mean ± SD: 28 ± 6, 173 ± 9, 69 ± 15, 6.57 ± 0.97, 6.24 ± 0.72, 5.46 ± 0.60, 5.25 ± 0.77, 5.25 ± 0.41, 5.44 ± 0.63, 6.51 ± 1.66, 6.40 ± 1.35

Values are means ± SD; n = 7. M, male; F, female; ES, supramaximal transcutaneous electrical phrenic nerve stimulation; CMS, cervical magnetic stimulation; I_{max}, maximal intensity; CW, clockwise current CMS; CCW, counterclockwise current CMS; Min and Max, minimal and maximal individual values observed for each listed parameter. P values are results of R-to-L comparison by using Student's paired t-test.
tude vs. stimulation intensity) was built to establish supramaximal stimulation. Right and left PNCTs were determined during bilateral ES, first with supramaximal intensity (IS), second at threshold intensity for M-w to appear (IL), and third at an intermediate intensity [IL = IL + (IL - IS)/2], CMS. The following procedure was applied for all subjects.

**STEP 1.** CMS was performed with the coil centered over the spinous process of the seventh cervical vertebra (C7) (Fig. 1), and the intensity was set to maximum (I\text{max}) with the current flowing clockwise. Slight position adjustments were made to obtain the best possible response in terms of M-w amplitude. A tightly fitting drawing of the internal circumference of the hole centering the coil was made on the skin by using a permanent marker. In this way, not only could the site of stimulation be safely retrieved but also the orientation of the coil and the degree of neck flexion could be accurately reproduced. Indeed, small changes in one or the other of these parameters visibly altered the fit of the skin drawing with the internal border of the central hole of the coil.

**STEP 2.** While coil position was maintained, stimulation intensity was decreased by using 5% intensity steps until M-w disappeared.

**STEP 3.** After stimulation intensity was brought back to maximum, the coil was flipped over to achieve counterclockwise stimulation.

**STEP 4.** Finally, with a return to clockwise current stimulation, the effects of moving the coil upward or downward were assessed for two positions in each direction (coil centered between C6 and C7 and over C6 in the upward direction, between C7 and T1 and between T1 and T2 in the downward direction).

In four subjects (subjects 1, 4–6), a simplified protocol was used on a separate day to examine the reproducibility of the measurements and to compare the pattern of response of surface and esophageal diaphragmatic EMG. This protocol consisted of simultaneous surface and esophageal recordings during supramaximal ES, C7 I\text{max} CMS, and C7 threshold CMS.

**Data Analysis and Statistics**

PNCTs were defined as the time elapsed between the stimulus and the onset of M-w, namely, the first negative departure of the signal from baseline (Fig. 2). M-w amplitudes were measured from peak to trough. Total M-w areas were measured from the onset of M-w to its end.

Statistical analysis was performed by using the SuperAnova software (Abacus Concepts, Berkeley, CA) on an Apple Macintosh computer. All differences were assessed with Fisher's protected least squares difference test after analysis of variance (ANOVA) for repeated measures (31). In all ANOVAs, the side of EMG recording provided one variable, and the other was the condition tested (namely, influence of stimulation technique, stimulation intensity, or coil position in the case of CMS). Reproducibility was tested by using cross-correlation analysis. Differences were considered significant when \( P < 0.05 \).

**Additional Experiments**

To examine some of the hypotheses suggested by the data and some possible confounding factors, two sets of additional experiments were conducted:

**Site of phrenic nerve depolarization (see DISCUSSION).** To modify the site of the interaction of the magnetic field with the phrenic nerve, magnetic stimulation was applied anteriorly in three subjects (subjects 1, 2, and 4) by placing the coil flat on the upper part of the sternum, with its upper extremity immediately above the suprasternal fossa. During these experiments, displacements of the abdomen in response to the stimulation were recorded by using a strain gauge. Two stimulation intensities were used (100 and 50% of I\text{max}). To allow comparison with the corresponding data obtained by using CMS, anterior stimulation was applied with the current flowing counterclockwise.

**Cross-talk from upper rib cage and neck muscles (see DISCUSSION).** Six male patients, aged 35 to 68 yr and suffering from amyotrophic lateral sclerosis (ALS), were studied by using ES and CMS (clockwise current stimulation and I\text{max} only). In addition to EMG recordings, upper rib cage and abdominal wall displacements in response to stimulations...
were studied by using strain gauges. These patients had severe ALS, with intense exertional dyspnea and dramatically reduced vital capacity and static inspiratory pressure (51.83 ± 14.48 and 34.00 ± 10.05% of predicted values, respectively). They exhibited signs of diaphragm paralysis, with an abdominal paradox during tidal breathing, voluntary deep inspirations, and in response to CMS. They also had hypertrophic inspiratory neck muscles, with an intense phasic inspiratory contraction (respiratory pulse) that was documented in three cases by surface EMG electrodes placed over the muscle mass of the sternomastoid muscles. In most cases, other muscles acting on the upper rib cage and possibly activated by CMS (trapezius muscles, 5 patients; pectoralis major muscles, 3 patients) (12) were not amyotrophic but rather seemed increased in volume and were unambiguously abnormally active during inspiration.

**RESULTS**

ES and CMS were both associated with typical EMG motor responses (Fig. 2).

**Electrical Stimulation**

With supramaximal ES, the right and left PNCTs were 6.57 ± 0.97 and 6.24 ± 0.72 ms, respectively. The right-to-left difference was not statistically significant (P = 0.26).

PNCTs tended to be slightly longer with decreasing ES intensity. However, a significant difference was noted only on the left side, between I5 and I1 (Fig. 3). As expected, decreasing ES intensity reduced M-w amplitude and area (Fig. 3).

**CMS**

At Imax, with clockwise current stimulation, the right and left cms-PNCTs were 5.46 ± 0.60 and 5.25 ± 0.77 ms, respectively. No significant right-to-left difference was observed (Table 2).

Changing the direction of stimulating current by flipping the coil over did not affect CMS-PNCTs (Table 2, Fig. 4) nor did it affect M-w amplitude. ANOVA showed no significant differences between clockwise and counterclockwise CMS-PNCTs obtained at Imax, but both were significantly shorter than supramaximal ES-PNCTs on a given side: the average difference was 1.05 ms (P = 0.0001) (Table 2, Fig. 5). Although statistical significance was never reached, side-to-side differences in PNCTs obtained with clockwise and counterclockwise CMS were present and consistent (Table 2), in accordance with corresponding changes in the flow of stimulating current respective to orientation of stimulated structures (Fig. 6).

Moving the coil up or down did not significantly modify CMS-PNCTs (Fig. 4). Conversely, M-w amplitude and total area significantly decreased when the coil was moved up: the values measured with the coil positioned over the C6-C7 junction and over C6 were much lower than the values measured with the coil in its standard C2 position (Fig. 4). M-w amplitude and total area did not differ from their C7 value when the coil was moved down. In some subjects, however, such a displacement was associated with higher amplitudes and greater areas (Fig. 4). It should also be noted that, when the coil was moved down, the natural curvature of the spine made it more vertical.

M-w amplitude decreased as CMS intensity decreased (Fig. 5). A bilateral response was present in all subjects at 65% Imax. This was also the case at 45% Imax for five subjects, at 35% Imax for three subjects, at 30% Imax for two subjects, and at 25% Imax for one subject. To limit the amount of missing data, the range of stimulation intensity used to build Fig. 5 and to compute the corresponding information was restricted to 45–100% Imax.

As CMS intensity decreased, PNCTs tended to increase (Fig. 5). This increase became significant for a CMS intensity of 65% Imax (5.78 ± 0.83 vs. 5.36 ± 0.67 ms, pooled right and left values, P = 0.02). At 45% Imax, CMS-PNCT was 6.54 ± 1.20 ms > Imax (pooled right and left values; 5 subjects) (P = 0.0001) but not

![Fig. 3. Effects of intensity of transcutaneous ES on phrenic nerve conduction time (PNCT; A), M-wave amplitude (B), and M-w area (area under curve; C). M-w amplitude and M-w area under curve are normalized to value obtained with supramaximal intensity (hatched bars) and hence are expressed without units. Solid bars, intermediate intensity; open bars, threshold intensity. Error bars, 1 SD. No significant difference was detected between right and left sides. Reducing stimulation intensity was associated with a slight increase in PNCT on left side, with a tendency for M-w amplitude to decrease, and, more obviously, with a reduction in M-w area. *Significantly different from bar to immediate left, P < 0.05. §Significant difference between supramaximal and threshold intensities, P < 0.05.](http://jap.physiology.org/)

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significantly different from the values obtained with supramaximal ES (CMS 6.54 ± 1.20 vs. ES 6.41 ± 0.84 ms, pooled right and left values). The average value of CMS-PNCT at threshold CMS intensities was 6.45 ± 1.45 ms, again not significantly different from supramaximal ES-PNCT.

CMS elicited a typical motor response in the abductor pollicis longus, probably via stimulation of the seventh cervical root. The latency of this response was 14.56 ± 1.07 ms at I_max (pooled left and right values) and did not vary significantly with decreasing CMS intensity (14.64 ± 1.32 ms at 45% I_max, pooled left and right values).

Esophageal Recordings of Diaphragmatic EMG

In the four subjects tested (the following results are average values of measurement in 8 phrenic nerves), the esophageal ES-PNCT was 6.64 vs. 6.88 ms with simultaneous surface electrode recordings. At I_max, the esophageal CMS-PNCT was 5.88 ms (simultaneous surface value 5.68 ms). At threshold CMS, the esophageal CMS-PNCT was 6.97 ms (simultaneous surface value 6.52 ms). Therefore, the PNCTs recorded with esophageal electrodes were not different from those recorded with surface electrodes, and the pattern of response of diaphragm esophageal EMG of the diaphragm appeared similar to that of surface EMG, with I_max CMS-PNCTs shorter than ES-PNCTs and threshold CMS-PNCTs longer than I_max CMS-PNCTs.

Reproducibility

In the four subjects studied twice for this study, cross-correlation analysis showed no significant between occasion differences between the values for surface ES-PNCT (6.58 ms on average on day 1 vs. 6.88 ms on day 2).
on day 2), $I_{\text{max}}$ CMS-PNCT (5.71 ms on average on day 1 vs. 5.68 ms on day 2), and threshold CMS-PNCT (6.62 ms on average on day 1 vs. 6.62 ms on day 2). Some subjects had participated in other studies conducted by using the same technique over the past 2 yr in our laboratory, with similar findings.

Additional Experiments

Anterior stimulation. In the three subjects tested with anterior magnetic stimulation, a typical bilateral motor response was observed (M-w) at both the stimulation intensities used (Fig. 2). This response was associated with an expansion of the abdominal wall, demonstrating diaphragm contraction. Latency was not clearly influenced by stimulation intensity and was consistently shorter than the shortest latency measured with CMS (4.6 and 3.3 ms, 4.4 and 4.8 ms, 4.4 and 4.2 ms, R and L side, subjects 1, 3, and 4, respectively).

ALS patients. For all patients studied, ES failed to elicit an diaphragm EMG response. This was also true for CMS, which was associated with neck muscle contraction and upper rib cage expansion synchronous with paradoxical inward movement of the abdominal wall.

DISCUSSION

The salient finding of this study is that PNCTs measured with CMS can be significantly shorter than PNCTs measured by using transcutaneous ES. This finding is at variance with recent reports (33) and somewhat surprising with regard to the hypothesis that CMS induces diaphragm contraction through stimulation of cervical motor roots (12, 30, 32, 33). Before an examination of possible explanations for this difference, it seems important to see our results in the perspective of available data.

Comparison With Other Studies

The average ES-PNCT reported in the present study (6.41 ± 0.84 ms, pooled right and left values) is in the range of previously exhibited values (Table 1). It tends to be on the lower end of this range (3), which is probably in line with the young age of our subjects and the correlation of PNCT with age noted by some investigators (3, 19). The right-to-left difference in PNCT, attributed by Delhez (8) to the difference in length between the right and left phrenic nerves, was not found in our investigation, nor was it consistently observed by others (17, 20, 23, 28).

A comparison of CMS results with data reported in the literature is much more difficult, however. Indeed, despite recent publication of data from the first large series of normal subjects (33), the amount of available CMS-PNCT data is far more limited than the amount of ES-PNCT data. Since its introduction in the field of respiratory muscle evaluation (30), CMS has mainly been used in studies dealing with diaphragm contractile properties: in addition to the previously quoted work by Zifko et al. (33), CMS-PNCTs data were provided for only four studies using CMS (4, 29, 30, 32). The average value for CMS-PNCTs in the present study (5.36 ± 0.67 ms, pooled right and left values, $I_{\text{max}}$ clockwise current stimulation) is lower than that reported in other studies (21, 33), including those performed by our own group (30). A careful evaluation of published data, however, shows that CMS-PNCTs below those generally accepted as the lower limit for normal ES-PNCT are not uncommon. It should also be noted that, compared with what is the case for ES, many of the technical aspects of CMS vary greatly among different laboratories because the technique is not yet standardized and continues to evolve. For example, stimulators have been rapidly gaining power since the introduction of CMS to study diaphragm function; various stimulators and coils are available, and these do not yield identical stimulating currents; experimental setups (coil positioning, stimulation intensity) may vary from one laboratory to the other. Such differences in the characteristics of the stimulators and in the experimental setup may explain differences in results obtained by our own group with CMS at a 7-yr interval (esophageal PNCTs shorter than surface PNCTs in our first CMS paper (30); no significant difference in the present study).

Conversely, a search of the Medline database for references to phrenic nerve conduction in normal human subjects yields some 70 articles, to which about 10 others published before 1966 must be added.
The recent work by Mills et al. (21) on unilateral magnetic stimulation (uMS) warrants particular attention. These researchers found a shorter PNCT with uMS than with ES applied at the same spot. This is consistent with our own findings and is not unexpected in view of the preferential recruitment of fast fibers by magnetic stimulation (25). The peak magnetic fields in the Mills et al. (21) study were very high (3.9–5.1 Tesla), which should further shorten PNCTs (see below) (1). Mills et al. (21) also noted that when diaphragm EMG was recorded from intradiaphragmatic electrodes in cardiac surgical patients, there was no difference between uMS-PNCT and ES-PNCT. This finding is perplexing and could cast doubt on the validity of surface diaphragm EMG recordings after magnetic stimulation (see below). However, PNCTs in the patients of Mills et al. (21) tended to exceed usual normal values and were markedly longer than these obtained in normal subjects in the same study (8.8 ms in patients with ES vs. 7.4 ms in normal subjects; 9.1 ms in patients with CMS, vs. 6.2 ms in normal subjects). Incipient phrenic nerve damage induced by cardiac surgery can, therefore, not be ruled out. Because fast fibers are more sensitive to such damage than slow ones (18), this could explain the absence of difference between uMS and ES after cardiac surgery.

Mechanisms for Differences Between ES- and CMS-PNCTs

If propagation of action potentials along a nerve has similar dynamics after electrical and magnetic stimulation, and if the source of diaphragm contraction after CMS is depolarization of cervical roots, CMS-PNCTs should be longer, not shorter, than ES-PNCTs. Indeed, the pathway to the diaphragm studied through CMS should theoretically be several centimeters longer than the pathway to the diaphragm studied through ES. Yet, the results we observed were diametrically opposed to this. In discussing these results, we have to consider two categories of phenomena: the first relates to possible confounding factors and the second to physiological mechanisms.

Technical confounding factors. With regard to EMG, the characteristics of diaphragm response to phrenic nerve stimulation can be affected by several factors: lung volume, site of recording, and position of recording electrodes, as well as posture of the subject (9, 19). In the present study, the site of recording and the position of the recording electrodes were identical for ES and CMS. Although lung volume was not very precisely controlled for, all stimulations were delivered at the end of a normal expiration, with the operator carefully observing the breathing cycle and asking the subjects to hold their breath briefly and relax at end expiration. Although slight variations in lung volume cannot be excluded, they are not likely to reach the magnitude of those used by Gandevia and McKenzie (9, 19) for studying the influence of lung volume on diaphragm EMG. The only noticeable difference between ES and CMS in our study was the position of the neck, which was kept straight for ES and bent forward slightly for CMS. We tried to minimize neck flexion for CMS, so this factor alone would not likely be sufficient to explain the change in length of the phrenic nerve and its roots that would account for a difference of >1 ms (see Physiological mechanisms). Neck flexion could result in some shortening of the phrenic nerve, but it should also lengthen the cervical roots.

Signal contamination. Because the magnetic field used to provoke diaphragm contraction via CMS is anything but focused, many other muscles besides the diaphragm are coactivated, either directly or via depolarization of their neighboring parent nerves. Laghi et al. (12) recently described EMG responses after CMS in muscles such as the sternomastoid, trapezius, and pectoralis major. Thus diaphragm M-w in response to CMS may be contaminated by action potentials arising in other muscles, which could affect both amplitude and latency (1). Although this possibility cannot be completely ruled out, there are several arguments against it. First, from a general point of view, the activation of extradiaphragmatic muscles does not necessarily mean that the corresponding compound muscle action potentials can contaminate the signal recorded by “diaphragm” surface electrodes. Indeed, when two recording EMG electrodes are placed very close to one another, they are much more likely to record near-field potentials than far-field potentials. In other words, the farther a muscle is from the electrodes, the less likely it is that its electrical activity will be picked up by the electrodes (2). For example, during unilateral phrenic nerve stimulation, contralateral diaphragm electrodes do not record the response of the stimulated hemidiaphragm. In addition, Laghi et al. (12) mentioned that M-w of the sternomastoid, trapezius, parasternal, and pectoralis muscles were not consistently recorded after either ES (not surprisingly) or CMS. Second, surface “diaphragm” electrodes were silent after CMS in the six patients with ALS that were specifically studied to address the issue of signal contamination. These patients had severely compromised innervation of the diaphragm, but this was not the case for their upper rib cage muscles (see METHODS). The CMS-related upper rib cage expansion associated with an inward movement of the abdominal wall indicates that CMS did provoke a strong contraction of upper rib cage muscles without diaphragm contraction. That the surface chest electrodes remained silent thus makes us confident that no EMG signal from muscles other than the diaphragm in response to CMS was detected. Third, the pattern of response of diaphragm esophageal EMG was similar to that of surface EMG, with 100% CMS-PNCT shorter than ES-PNCT (6.64 vs. 5.88 ms, respectively, for esophageal recordings; 6.88 vs. 5.68 ms, respectively, for surface recordings) and 50% CMS-PNCT longer than 100% CMS-PNCT (6.97 vs. 5.88 ms, respectively, for esophageal recordings; 6.52 vs. 5.68 ms, respectively, for surface recordings). The possibility that an esophageal recording of diaphragm M-w be contaminated by action potentials arising in extradiaphragmatic muscles activated by CMS is extremely remote. Thus the pattern of response that we observed
with this type of electrode is a strong argument against "contamination" explaining the shorter PNCT with CMS than with ES. It also rules out the hypothesis that the increase in PNCT with decreasing CMS intensity be the result of a decreased coactivation of extradiaphragmatic muscles.

Physiological mechanisms. For any given site of stimulation, magnetic stimulation (as opposed to electrical) preferentially recruits fast fibers. This could at least partially account for our results. A major argument for the preferential recruitment of fast fibers during CMS, however, is based on the fact that there is no significant shift of onset latency-to-muscle action potential when stimulation intensity is changed (4, 5).

In our investigation, we observed the opposite pattern for the diaphragm (Fig. 5): there was marked shortening in PNCT as CMS intensity increased. This argues against stimulation at the level of the roots. Indeed, with magnetic stimulation, excitation of peripheral nervous structures takes place where the nerve bends or near regions with decreased field homogeneity (15). Cervical roots change direction when they leave the intervertebral foramen, in which it has been shown that the first spatial derivative of the electric field stimulation produced by magnetic stimulation is at its maximum (16). Thus it is believed that the site of CMS-induced depolarization of cervical roots is fixed and very focused, corresponding to the short intraraminal segment (22). As a consequence, the latency-to-motor action potential after nonfocal CMS is not especially sensitive to changes in intensity or to changes in coil position (4, 5, 16). The fixed latency of the abductor pollicis longus M-w that we observed agrees with such findings (see RESULTS). On the other hand, the decrease in CMS-PNCT as stimulation intensity increases is compatible with stimulation of the trunk of a nerve because magnetic stimulation causes the virtual cathode to become more distal as stimulation intensity increases (24).  

If CMS excites the phrenic nerve itself rather than the corresponding roots, then it is easier to understand why CMS-PNCTs are shorter than ES-PNCTs. Studies comparing magnetic stimulation with electrical stimulation of peripheral nerves (1, 13, 25, 27) have shown that action potential latencies determined magnetically can be much shorter than electrically determined ones (25), mainly because during magnetic stimulation the virtual cathode can be quite distant from the vascular anode (1). Moreover, and probably more importantly, CMS, as initially described (30) and used in this study, is possibly able to stimulate the phrenic nerve at a more distal point along its path than at the neck, where ES stimulates it. Figure 7 illustrates the way this may come about. Here it can be seen that a sufficiently powerful magnetic field relative to the subject's morphology can reach the phrenic nerve at the anterior part of the thorax. Given the position of the subject and the type of coil, the stimulation should occur at approximately the level of the first intercostal space.

Several arguments support this hypothesis. First, the distance between the supposed site of intrathoracic phrenic nerve stimulation and the ES spot in the neck was 6–8 cm in our subjects. If human phrenic nerve velocity is 78 m/s as measured in one cadaver by Heinbecker et al. (11) (this seems to be the only such information available in the literature), the distance nicely accounts for the average 1.05-ms difference between ES-PNCT and CMS-PNCT, with the approximation corresponding to the particularities of magnetic stimulation already mentioned (fast fibers' preferential recruitment and distal virtual cathode). It is interesting to note that the difference between ES-PNCT and CMS-PNCT was less pronounced (or was in inverse relation to the average behavior) in heavier subjects (Table 2). Second, anterior magnetic stimulation, which should have depolarized the nerve at a lower point in the thorax, resulted in shorter latencies, and the difference was again compatible with the distance separating the two putative points of stimulation. Third, having used CMS in our laboratory for several years, we have observed that CMS-PNCTs tended to become shorter with time. This may be the result of the increase in power of the stimulators, leading to an increased distance between the anode and the cathode (1, 24). Although the differences in fiber recruitments by ES and MS can influence the shape of the corresponding M-w, analysis of some of our data in terms of time to

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3 We also observed changes in ES-PNCTs with ES intensity that were significant on the left side in spite of the small size of the studied sample (Fig. 3). Stimulation intensity is seldom mentioned in phrenic nerve conduction studies (Table 1), but attention should be paid to this factor, particularly with regard to follow-up of phrenic nerve lesions and more generally for standardization of respiratory muscles tests.
first and second peak of the diaphragm M-w showed a consistent trend (shorter times to peaks with CMS than with ES). This supports the idea of a more distal depolarization of the phrenic nerve by CMS, and is a supplemental argument against signal contamination.

The above hypothesis may also be a way to reconcile our findings with those of others and to explain some peculiar aspects of our results. Chokroverty et al. (5), using a different stimulator equipped with a small circular coil positioned higher than ours in a lateral rather than median position, have stimulated C4-C5 and obtained diaphragm action potentials in which latency was independent of stimulation intensity and unaffected by moving the coil up or down. These results are typical of actual root stimulation (4, 16). In our study, not only did CMS intensity influence CMS-PNCTs (Fig. 5) but also moving the coil over the vertebral column modified the latency and the amplitude of the responses (Fig. 4). The discrepancy between the two patterns is easily explained if the cervical roots were the origin of the diaphragm contraction in the study by Chokroverty et al. (5) and the phrenic nerve itself in our study. The reason why moving the coil down did not shorten CMS-PNCTs in our investigation may have been because the downward displacement was associated with some degree of vertical rotation. Such a movement of the coil in a circular arc should not change the point of phrenic nerve excitation (Fig. 7). Zifko et al. (33), using a stimulator and a coil very similar to ours, obtained latencies longer than the one measured at $I_{\text{max}}$ in our study. However, these authors used only low-intensity stimulation, 60% of their stimulator’s maximal output. It is thus conceivable that the magnetic field they obtained was not capable of producing stimulating currents in the vicinity of the phrenic nerve at the anterior part of the thorax. The longer latencies measured by Zifko et al. (33) could thus either relate to root stimulation or express effects of CMS intensity on CMS-PNCTs (Fig. 5 in our study). With this in mind, the latencies reported by Zifko et al. (33) are very close to those measured at threshold intensities in our subjects.

Practical Consequences and Conclusions

As shown in Table 1, and with the assumption of the restriction of stimulation intensity already mentioned (see footnote 2), ES-PNCTs do not vary much among different laboratories or over time. This is not true for magnetic stimulation. Indeed, reported PNCTs are different with unilateral phrenic nerve stimulation (21), lateralized root stimulation (5, 33), or “classic” CMS (present study). Standardization is thus needed before values can be accurately compared among studies. This is also needed to establish normal values, which should take into account the possible effects of age and height, two factors that could influence PNCT (3, 19).

Before guidelines are established, each laboratory should carefully standardize its own technique and establish its own set of normal values before using magnetic stimulation in clinical investigation. For electrophysiological follow-up of phrenic nerve dysfunction, it is crucial that the technique used in a given patient be exactly the same over time. The elements to be standardized are not only coil positioning and stimulation intensity (see below) but also the direction of the stimulating current. Changing this direction can result in a change of onset latency that can reach 0.5 ms (1). Latency is shorter when the stimulating current flows from the proximal to the distal ends of the nerve. In this regard, it should be noted that to evoke maximum action potential, the induced current must flow along the course of the nerve. In summary, if, in a determination of PNCT, classic CMS (large doughnut-shaped coil centered over $C_7$) is chosen to obtain simultaneous contractions of both hemidiaphragms (whether for its ease of use or because diaphragm contractile properties are to be studied), investigators should 1) make every effort to standardize coil positioning and subject posture; 2) study the right PNCT with clockwise current stimulation but flip the coil to study the left PNCT; and 3) use supramaximal stimulation or the maximal possible stimulation intensity rather than threshold stimulation, as recommended for nerve conduction studies using electrical stimulation (2). With regard to this issue, it is important to note that the notion of supramaximal stimulation with CMS should remain EMG based. Indeed, the diaphragm being the only muscle to contract in response to ES, a transdiaphragmatic pressure (Pdi) recruitment curve should plateau for stimulation intensities comparable to that associated with a plateau in the EMG response. Recording the EMG would then not be mandatory to verify that ES is supramaximal. This is not the case with CMS, in which the contraction of extradiaphragmatic muscles enhances the efficacy of the diaphragmatic contraction independently of the degree of electrical activation of the diaphragm (12, 29). A plateau in CMS-Pdi can thus be impossible to observe despite an actual supramaximal stimulation.

These precautions taken, we believe that classic CMS can be a useful and reliable tool to study PNCT. CMS and lateralized root stimulation (5, 33) could complement each other, opening the possibility of distinguishing a conduction abnormality because of a lesion of the phrenic nerve itself (CMS) or of its roots (5, 33). The usefulness of anterior magnetic stimulation remains to be determined, but this technique could be useful when there is reasonable doubt about the ability of CMS to reach the phrenic nerve trunk anteriorly. Such doubt could arise when seemingly long PNCTs values are found with CMS, or when CMS and lateralized stimulation provide similar figures in a given patient.

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