

Determination of Maximal Diaphragm Strength in Chronic Obstructive Pulmonary Disease: Cervical Magnetic Stimulation Versus Traditional Sniff Maneuver

Juana Martínez-Llorens,^a Carlos Coronell,^a Alba Ramírez-Sarmiento,^a Mauricio Orozco-Levi,^a Josep M. Espadaler,^b Juan Bautista Gáldiz,^c and Joaquim Gea,^a on behalf of the ENIGMA COPD study group

^aServei de Medicina Respiratòria, Unitat de Recerca en Múscul i Aparell Respiratori (URMAR), Hospital del Mar-IMIM, Departament CEXS, Universitat Pompeu Fabra, Barcelona, Spain.

^bSecció de Neurofisiologia, Unitat de Recerca en Múscul i Aparell Respiratori (URMAR), Hospital del Mar-IMIM, Departament CEXS, Universitat Pompeu Fabra, Barcelona, Spain.

Servicio de Neumología, Hospital de Cruces, Barakaldo, Vizcaya, Spain.

Study supported by UE QLRT-2001, RTIC C03/11 (Red RespiraISCIII) and SOCAP 2002 and 2003 grants.

OBJECTIVE: Magnetic stimulation of the diaphragm allows its strength to be assessed. The clinical applications of this technique are becoming more widespread given that the patient's cooperation is not required. The aim of the present study was to compare this inhalation technique with traditional voluntary forced inspiration (sniff test) in a group of patients with chronic obstructive pulmonary disease (COPD).

PATIENTS AND METHODS: Sixteen men with moderateto-severe COPD were studied (mean [SD] forced expiratory volume in 1 second, 35% [15%] of the reference value). For all patients, the maximal transdiaphragmatic pressure (a measure of the contractility of the muscle) was determined at peak inspiration and during cervical magnetic stimulation.

RESULTS: A moderate correlation between measurements with the 2 techniques was observed. The value obtained with stimulation was approximately 20% of that obtained with voluntary inhalation (22 [7] cm H₂O vs 97 [27] cm H₂O, respectively). The stimulation technique yielded an intraindividual coefficient of variation of 12% (7%) and an interindividual one of 33% (6%). Very similar values for these coefficients were obtained with forced inhalation. Qualitative analysis of the stimulation technique showed it to have a high sensitivity (89%) for diagnosing muscle weakness, with few false negatives. In contrast, specificity was very low (43%), and false positives for muscle weakness were relatively common. The overall effectiveness of the prediction was acceptable (69%).

CONCLUSIONS: Cervical magnetic stimulation appears to be a good clinical option for ruling out diaphragm weakness. It is particularly indicated in patients with limited capacity for understanding instructions or those unable to cooperate.

Key words: *Respiratory muscles. Pulmonary disease. Transdiaphragmatic pressure. Muscle stimulation.*

Servei de Medicina Respiratòria. Hospital del Mar.

Pg. Marítim, 27. 08003 Barcelona. España.

E-mail: jmartinezl@imas.imim.es

Fuerza máxima del diafragma en la EPOC: estimulación magnética cervical frente a la clásica maniobra de inhalación forzada

OBJETIVO: La estimulación magnética del diafragma es una técnica que permite evaluar la fuerza de este músculo. Dado que obvia la necesidad de colaboración del paciente, va extendiendo progresivamente su aplicación clínica. El objetivo del presente estudio ha sido comparar esta técnica de estimulación con la clásica de inhalación voluntaria forzada (*sniff*) en un grupo de pacientes con enfermedad pulmonar obstructiva crónica (EPOC).

PACIENTES Y MÉTODOS: Se estudió a 16 pacientes varones con EPOC de moderada a grave (valor medio \pm desviación estándar del volumen espiratorio forzado en el primer segundo del 35 \pm 15% del valor de referencia). En todos ellos se obtuvo la presión máxima del diafragma (expresión de la fuerza contráctil del músculo) por maniobras de inhalación voluntaria máxima y de estimulación cervical magnética.

RESULTADOS: Se observó una relación moderada entre ambas técnicas, siendo los valores obtenidos con estimulación de aproximadamente un 20% de los obtenidos con la maniobra voluntaria (97 ± 27 y 22 ± 7 cmH₂O, respectivamente). La técnica de estimulación mostró unos coeficientes de variabilidad intraindividual del 12 ± 7%, e interindividual del 33 ± 6%, muy similares a los del método de inhalación. El análisis cualitativo de la técnica de estimulación para el diagnóstico de debilidad muscular mostró una elevada sensibilidad (89%), con escasos falsos negativos. Por el contrario, su especificidad fue muy baja (43%), con una tasa relativamente elevada de sobrediagnósticos. La eficacia de la predicción resultó globalmente aceptable (69%).

CONCLUSIONES: La técnica de estimulación magnética cervical se muestra como una buena opción clínica para descartar debilidad del diafragma, con indicación sobre todo en pacientes con poca capacidad de comprensión o incapacidad de colaboración.

Palabras clave: Músculos respiratorios. Enfermedad pulmonar. Presión transdiafragmática. Estimulación muscular.

Dr J. Martínez-Llorens received the SEPAR 2002 grant during the study period. Correspondence: Dra. J. Martínez-Llorens.

Manuscript received August 31, 2005. Accepted for publication, February 28, 2006.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is generally progressive and not completely reversible.¹⁻⁴ Its pathogenesis is closely related to the inhalation of toxic particles or gases, particularly cigarette smoke.¹ Traditionally, the disease was thought to affect only the pulmonary parenchyma and the bronchial tree. Recently, however, closer attention has been paid to other affected organs and body systems that are often distant from the primary site. These are the so-called systemic effects of COPD and are taken to include processes such as general inflammation and oxidative stress, nutritional disorders, contractile and endothelial dysfunction, and poor regulation of certain signaling molecules.⁵⁻⁷ The changes that take place affect the cardiovascular system, striated muscle, blood, kidneys, central nervous system, and even bone tissue in addition to the lung. $^{\rm 8-14}$ The general loss of muscle mass and associated dysfunction are probably the most widely studied systemic consequences of COPD, and such processes may even influence prognosis.15,16

There is a group of highly specialized muscles whose purpose is to ensure good pulmonary ventilation. These muscles are known as respiratory muscles and they work mainly during the active part of the respiratory cycle, that is, inspiration. In addition to the aforementioned systemic factors, inspiratory muscles in COPD patients are subject to a series of negative influences that arise from changes in the respiratory system due to the disease.^{5,7} For example, airway resistance is high in patients with COPD, and the muscles have to work harder. Unfortunately, the diaphragm, which is the main inspiratory muscle, is a long way from its optimum contractile length as a result of pulmonary hyperinflation. Additionally, muscles have to work harder in worse conditions, as the oxygen and nutrient supply is often compromised in patients with COPD. Unsurprisingly, a muscle may begin to fail in such situations, becoming weaker, less resistant, and more susceptible to fatigue.

Measurement of the maximum strength of the respiratory muscles is extremely useful in clinical practice, both to help detect muscle weakness or dysfunction, and for monitoring and assessing the efficacy of a variety of therapeutic interventions.^{17,18} Although the overall strength of the inspiratory muscles is easy to determine in clinical practice by measuring the maximal inspiratory mouth pressure, techniques for specific determination of the strength of the diaphragm are somewhat more complicated. All these techniques require measurement of intrathoracic and abdominal pressure to calculate the so-called transdiaphragmatic pressure (Pdi),^{19,20} and so they are relatively invasive. The Pdi is obtained by calculating the difference between the readings for intrathoracic and abdominal pressures.²⁰ It can be determined both during normal breathing and at maximum effort. In the latter instance, when the value would reflect the maximum contractile strength of the muscle, a range of forced maneuvers,

both static (with no airflow) and dynamic (with flow), are available. The most widely used inhalation maneuver is dynamic and consists of forced inhalation from residual functional capacity or residual volume, the so-called sniff maneuver from which Pdi_{sniff} is determined.^{19,20} In general, a value less than 100 cm H₂O is taken as indicative of weakness or fatigue of the diaphragm.²¹ However, there is an important problem with the sniff maneuver (and indeed with most other respiratory function tests): it depends on the extent to which the subject understands the instructions and cooperates. Therefore, the actual strength of the diaphragm may be underestimated.

It is also possible to induce maximal or submaximal involuntary contraction of a muscle by stimulating the muscle itself or the nerve structures that regulate its activity.²¹ In the past, bilateral electrical stimulation was used. However, this technique is painful and uncomfortable for the patient. In the last decade, several groups, including our own, have developed magnetic stimulation to obtained a response of the diaphragm.²²⁻²⁶ Currently, one of the most widely used approaches in clinical practice is cervical magnetic stimulation.^{21,22,27-29}

The aim of our study was to compare Pdi_{sniff} to the value obtained by cervical magnetic stimulation (Pdi_{twitch}) in patients with moderate-to-severe COPD, as well as to assess the variability in these measurements.

Patients and Methods

Patients

The sample size calculation was based on previous studies of the transcranial magnetic stimulation technique by our group. The present study included a total of 16 male patients with moderate-to-severe COPD, that is, with a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity less than 70% and FEV₁ less than 80% of the reference value,¹ in a stable phase in the 3 months prior to the study. Patients were sequentially recruited from the outpatient pharmacy of the respiratory function unit for care of patients with COPD. Exclusion criteria were regular alcohol intake (>100 g/day) or drug abuse, presence of neoplastic, endocrine, psychiatric, or severe orthopedic disease, as well as concurrent presentation of muscular and neurological disease, or the presence of sequelae from cerebrovascular accidents. Those who had difficulty cooperating and those who were receiving medical treatment that might have affected muscle function and structure (for example, systemic corticosteroids, calcium channel blockers, etc) were also excluded. All patients were informed of the aims of the study and all gave informed consent in writing. The study was approved by the ethics committee of our hospital.

Methods

All patients underwent forced spirometry testing (Datospir 500, SIBEL, Barcelona, Spain), in accordance with the guidelines and the reference values of the Spanish Society for Pulmonology and Thoracic Surgery (SEPAR).³⁰ Static lung volumes and airway resistances were then determined by body plethysmography (Masterlab, Jaeger, Würzburg, Germany), using the reference values published for the Mediterranean population.³¹ Likewise, the carbon monoxide diffusing capacity was determined with a gas analyzer fitted to the aforementioned equipment, using the single-breath

MARTÍNEZ-LLORENS J ET AL. DETERMINATION OF MAXIMAL DIAPHRAGM STRENGTH IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: CERVICAL MAGNETIC STIMULATION VERSUS TRADITIONAL SNIFF MANEUVER

technique and reference values from the Mediterranean population.³² Arterial blood gases were determined with a conventional polarographic analyzer (RapidLab 860, Chiron/Diagnostic, Wuppertal-Bramen, Germany).

The overall voluntary strength of the respiratory muscles was obtained by measuring the maximal mouth pressures. These measurements were taken with a flanged mouthpiece (SIBEL) with a narrow orifice to minimize the participation of the buccinator muscle. To determine the maximal inspiratory mouth pressure, the patients performed the maneuvers from residual volume, whereas the maximal expiratory pressure was measured at total lung capacity. The highest reading from 3 valid and reproducible maneuvers (difference <5%) was included in the analysis. The mouthpiece was connected to a pressure manometer (TSD 104, Biopac Systems, Goleta, CA, USA), and the signal recorded with a digital polygraph (Biopac Systems). The values of maximal mouth pressure and maximal expiratory pressure were expressed relative to reference values for a Mediterranean population.³³

We then determined the specific strength of the diaphragm. First, esophageal and gastric probes were put in place under nasal anesthetic (Figure 1). The patient breathed normally until the respiratory pattern stabilized. The sniff maneuver or induced maneuvers were then performed, in random order. The sniff maneuver consisted of forced inhalation at residual functional capacity (Pdi_{sniff}). Involuntary strength of the diaphragm was measured with a Magstim 200 stimulator (Magstim Co. Ltd., Whitland Dyfed, Wales, United Kingdom), at a maximum field strength of 2.5 T using a 90-mm coil. The coil was placed on the nape of the neck, with the head bent forwards and with the axis of the stimulator over the C5-C7 spinous processes (Figure 2). Stimulation was applied with the stimulator at full power and, as before, at residual functional capacity (Pdi_{twitch}). At least 3 valid maneuvers (defined as those with a percentage deflection from the pressure curve of less than 10% between maneuvers) were performed with both techniques for all patients.

Statistical Analysis

Quantitative variables were presented as means (SD). To calculate the 2 maximum Pdi values, the highest value obtained with each technique was used, whereas for calculation of variability, 3 valid maneuvers were used in each case. The relationship between the different quantitative variables was analyzed with the Pearson coefficient. In all cases, statistical significance was defined as an α error (*P*) less than .05. The coefficient of variability was calculated according to the formula: (SD/mean)×100. The specificity, sensitivity, positive and negative predictive values, diagnostic likelihood ratio, and the predictive power and error in the prediction were calculated for both techniques. In each case, the alternative technique was taken as the standard, with the cutoff points for diagnosis of reduced diaphragm strength being 100 cm H₂O for Pdi_{sniff}²¹ and 23 cm H₂O for Pdi_{twitch}.³⁴

Results

The main demographic characteristics, nutritional state, and lung and muscle function variables are presented in Table 1. The study population consisted of patients with moderate-to-severe COPD (mean [SD] FEV₁, 35% [15%] of predicted), air trapping, a slight-to-moderate reduction in carbon monoxide transfer, mild-to-moderate hypoxemia, and absence of



Figure 1. Schematic diagram of where different ventilatory pressures for determining diaphragm strength or overall strength of the respiratory muscles are measured.



Figure 2. Simulation of the magnetic cervical diaphragm stimulation with a volunteer.

hypercapnia. The nutritional state was still acceptable (body mass index, 26.5 [3.6] kg/m²), but patients showed slight-to-moderate muscular dysfunction of both inspiratory and expiratory muscles. It was possible to readily obtain a diaphragmatic signal in all patients with the sniff maneuver and magnetic stimulation techniques–the reproducibility of the 2 techniques is shown in Tables 2 and 3, respectively. The mean value for Pdi_{sniff} was 97 (27) cm H₂O (range, 58-155 cm H₂O). The maximum change in valid Pdi_{sniff} maneuvers was 31%, and the intraindividual coefficient of variability for this maneuver was 8.9% (4.7%) (range, 2.4%-20.9%). The interindividual coefficient of variability

TABLE 1 Anthropometric, Pulmonary, and Respiratory Muscle Characteristics of the Patients with COPD*

No. of patients	16
Age, y	69 (7)
Weight, kg	74 (8)
BMI, kg/m ²	26.5 (3.6)
FEV ₁ /FVC, %	44 (12)
FEV, % predicted	35 (15)
TLC, % predicted	103 (17)
RV/TLC, %	63 (11)
DL _{co} , % predicted	67 (22)
KCO, % predicted	77 (23)
Pm, % predicted	68 (12)
MEP, % predicted	73 (22)
PaO ₂ , mmHg	73 (11)
PaCO ₂ , mmHg	44.6 (3.6)
Pdi_{sniff} , cm H ₂ O	97 (27)
Pdi_{twitch}, cmH_2O	22 (7)

*Values expressed as mean (SD).

Values expressed as mean (SD). BMI indicates body mass index; FEV, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DL_{cO} , diffusing capacity of the lung for carbon monoxide; KCO: ratio of DL_{cO} /alveolar volume; Pm, peak mouth pressure; MEP, maximal expiratory pressure; Pdi market the readiant pressure; DEP, maximal expiratory pressure; Pdi surged in the control of monoxide; RDC is the control of the control of the readiant pressure; Pdi surged in the control of the co transdiaphragmatic pressure from the sniff maneuver; Pdi_{twitch}, transdiaphragmatic pressure from cervical stimulation.

TABLE 2 Summary of the Variability of Transdiaphragmatic Pressure Obtained by the Sniff Maneuver During 3 Maneuvers in the Patients Studied

Patient	Pdi _{sniff} 1 (cm H ₂ O)	Pdi _{sniff} 2 (cm H ₂ O)	Pdi _{sniff} 3 (cm H ₂ O)
1	65	67	60
2	128	102	115
3	107	103	112
4	53	57	58
5	80	65	66
6	89	85	76
7	99	118	106
8	43	62	44
9	126	141	155
10	84	110	108
11	75	61	70
12	122	128	122
13	82	86	84
14	78	91	79
15	75	73	83
16	95	110	89
Mean (SD)	87 (25)	91 (26)	89 (29)

*Pdisniff indicates transdiaphragmatic pressure obtained by the sniff maneuver.

was 28.9% (1.1%) (range, 28.1%-30.2%). The mean value of cervical Pdi_{twitch} was 22 (7) cm H₂O (range, 10-40 cm H_2O), corresponding to values approximately 20% of those obtained with the sniff maneuver. In this case, the maximum change was 39%, with an intraindividual coefficient of variability of 11.6% (6.9%) (range, 2.0%-25.0%) and an interindividual coefficient of variability of 32.6% (5.9%) (range, 27.0%-38.7%). No statistically significant differences were found between the 3 valid maneuvers for either Pdi_{sniff} (87 [25] cm H₂O vs 91 [26] cm H₂O and 89 [29] cm H_2O or for cervical Pdi_{twitch} (20 [5] cm H_2O vs 20 [6] cm H_2O and 19 [7] cm H_2O). The sensitivity and

512 Arch Bronconeumol. 2006;42(10):509-15 specificity results for the 2 techniques are presented in Table 4. In short, with the sniff test as the reference maneuver, magnetic cervical stimulation was out by 31% (error in the prediction), and failed to diagnose only 6% of the patients with diaphragmatic dysfunction while falsely diagnosing up to 25% in patients with no such physiological abnormality. In contrast, with magnetic stimulation as the reference technique, the sniff maneuver (with an implicit error in this type of analysis of 31%) failed to diagnose the condition in 25% of the patients and falsely diagnosed it in 6%.

The correlation between the values obtained with the 2 techniques was no stronger than moderate, as can be seen in Figure 3. In contrast, a significant correlation was observed between the strength measured with the sniff maneuver (Pdi_{sniff}) and both the severity of bronchial obstruction (represented by FEV_1 , r=0.615, P=.019) and the extent of air trapping (residual volume/total lung capacity, r=-0.942, P<.001). That is, patients with the most severe COPD also had a weaker diaphragm. No correlations of interest were found between lung function and the values obtained with magnetic stimulation of the diaphragm.

TABLE 3 Variability of Transdiaphragmatic Pressure Obtained by Magnetic Cervical Stimulation During 3 Maneuvers in Patients With COPD*

Patient	Pdi _{twitch} 1 (cm H ₂ O)	Pdi _{twitch} 2 (cm H ₂ O)	Pdi _{twitch} 3 (cm H ₂ O)
1	20	18	12
2	16	13	16
3	14	13	13
4	23	21	22
5	21	24	23
6	19	16	14
7	23	27	24
8	10	7	8
9	33	34	40
10	24	15	19
11	26	26	26
12	20	22	16
13	17	22	23
14	22	20	17
15	18	16	17
16	15	19	16
Mean (SD)	20 (5)	20 (6)	19 (7)

^{*}Pdi_{twitch} inc stimulation. indicates transdiaphragmatic pressure obtained by magnetic cervical

TABLE 4
Comparison of the Diagnostic Validity of Each Technique
for Measuring the Transdiaphragmatic Pressure With
Reference to the Alternative Technique

	Magnetic Stimulation	Sniff Maneuver
Specificity	43%	75%
Sensitivity	89%	67%
Positive predictive value	67%	89%
Negative predictive value	75%	43%
Diagnostic likelihood ratio	1.56	2.68

Discussion

The most important findings of the present study were the relative ease with which a valid reading can be taken with both techniques, and the acceptable and similar internal reproducibility obtained. However, the relatively weak correlation between the values obtained with each technique stands out, with the mean difference between the 2 being similar to that reported in the literature. The clinical effectiveness of magnetic stimulation is high, due in particular to its high sensitivity.

It is well known that the effective strength of the diaphragm is lower in patients with COPD than in healthy subjects.³⁵ The most important factor implicated in this functional abnormality seems to be hyperinflation of the lungs, which flattens and shortens the diaphragm, and so it is no longer near its optimum contractile length.³⁶ Moreover, the mechanics dictate that the costal and crural parts of the muscle no longer contract "in parallel" (the ideal situation, in which the total strength of the muscle is equivalent to the vectorial sum of the strength of its parts), but rather do so "in series" (in which the actions of the different parts of the muscle are no longer additive).³⁷ As expected, the extent of air trapping correlated with the severity of diaphragmatic muscular dysfunction detected by the sniff maneuver. This abnormality has also been attributed to local factors such as metabolic imbalance between supply and demand in a muscle working under increased loads, but with poor energy supply.^{5,7} Other factors have also been described that favor diaphragmatic dysfunction. Unlike the factors discussed earlier, many of these factors would apply to all the muscles of the body and would contribute to systemic muscular dysfunction. Examples include undernutrition, other concurrent diseases and old age, the use of drugs that damage the muscle, and systemic and local inflammation and oxidative stress in the muscle itself.^{5,6} Structural and molecular changes in the diaphragm of the patients with COPD would lead to smaller fibers than in subjects free of pulmonary disease,^{38,39} destruction of sarcomeres,⁴⁰ occasional presence of structural disorders in diaphragmatic mitochondria,⁴¹ and oxidation of a variety of structural and enzymatic proteins.42 However, these disorders coexist with adaptive structural changes,43,44 as shown in an elegant study published by Similowski et al³⁶ almost 10 years ago. According to that study, patients with COPD have even greater diaphragm strength than healthy subjects who made an effort to maintain hyperinflated lungs to ensure similar lung volumes to those of COPD patients.

Once respiratory muscle dysfunction and the role of some of the factors implicated in its pathogenesis had been established by a range of investigators in patients with COPD, attention turned to the more clinical problem of how to measure this dysfunction. In general, this is resolved by measuring mouth pressures, for which reference values are available. These measurements give a good estimate of the general strength of the respiratory muscles. Techniques have also been developed that allow airway resistance to be measured, but in this case, there



Figure 3. Relationship between maximum transdiaphragmatic pressures obtained by the sniff maneuver (Pdi_{sniff}) and cervical stimulation (Pdi_{twitch}) in study patients. Note also the position of each point relative to the cutoff points for diaphragm weakness with the 2 techniques used. Grey circles represent patients erroneously classified according to one or the other technique, with the alternative technique used as the reference.

are no well-established reference values. However, it is often necessary to specifically assess the strength of the diaphragm. To do this, maximal sniff maneuvers can be performed. These, in combination with the Pdi reading, allow the maximum strength of the muscle to be estimated, but because the maneuvers are voluntary, the results are overly dependent on the patient's motivation and ability to cooperate. Therefore, alternative methods have been assessed to dispense with the need for such cooperation. To this end, and after variable results with electrical stimulation, which is uncomfortable and painful, other techniques have been developed in recent years for stimulating the diaphragm. One such technique is magnetic stimulation applied to either the cerebral cortex or the nape of the neck.²²⁻²⁹ Investigators have also attempted to reduce the invasive nature of measurements of respiratory pressures by using nasal and oropharyngeal measurements (as an approximate measure of intrathoracic pressure) and intravesical pressure (intra-abdominal pressure).45,46 Experience with techniques of magnetic stimulation of the diaphragm is still limited, and only a few groups throughout the world practice such techniques. In Spain, Gáldiz et al²⁶ published a study 2 years ago in which bilateral anterolateral magnetic stimulation, often known by its abbreviation, BAMS, and posterior cervical magnetic stimulation were compared in a group of healthy subjects. The predictive power of measurements with the 2 techniques was similar and the variability of the measurements was acceptable. In the present study, we aimed to compare cervical stimulation, which is relatively easy to apply in clinical practice, with the most widely used technique for assessment of the diaphragm strength-the traditional sniff maneuver. The study was carried out in patients with COPD because we consider such patients to be the prime candidates for clinical application of the stimulation technique. In our

population, the strength of the diaphragm measured by stimulation was similar to that described previously in the biomedical literature in both Spanish and English.^{22,24-27,34} Moreover, the values obtained with the stimulation technique were approximately 20% those generated by the sniff maneuver, as in previous studies.^{21,34,47} The presence of broad interindividual variability for the pressure obtained by stimulation and with sniff maneuvers in both healthy subjects and patients with COPD has also been reported in all studies that assess diaphragm strength.^{19,22,24-29} This variability is not only observed for cervical stimulation but also for stimulation at other sites, for example bilateral anterolateral stimulation.48,49 Interindividual variability in both healthy subjects and patients with COPD can be explained by anthropometric differences and sex differences between individuals. Currently, an important drawback of magnetic stimulation is the lack of validated reference equations. Furthermore, in the specific case of patients with COPD, the observed variability can also be explained by the fact that only some patients will have a clearly reduced diaphragm strength. Our group's recent findings seem to suggest that these patients have greater deficiency in the buffering of oxidizing radicals in the respiratory muscles.⁴² The intraindividual variability in our patients is similar or only slightly greater than that described for other series of healthy subjects.^{26,34} We have only found 1 study that analyzes this parameter in patients with COPD.47 In that study, the coefficient of variability was somewhat smaller than in the present study (9%). Of note is the relatively weak correlation between quantitative values measured with the 2 techniques investigated in the present study compared to previous ones, which reported a stronger correlation.47,50 However, the findings of a qualitative analysis to determine whether or not muscle weakness is present (one of the main aims of the present study) were much more promising. In such an analysis, magnetic stimulation proved highly sensitive, with few false negatives although specificity was low-false diagnosis of diaphragm weakness was relatively frequent. The overall predictive power was, nonetheless, acceptable.

The present study had no control group of healthy volunteers as the 2 techniques had already been compared in such a population in previous studies,^{22,26,34} and our objective was to study patients with COPD. In such patients, changes can appear in the origin or transmission of nerve impulses controlling breathing, as well as in the extent of muscle recruitment,^{36,51} so specific studies would be needed.

As an intellectual exercise, we also assessed the most widely used technique for evaluating diaphragm strength, namely, determination of the pressure generated by the diaphragm during a sniff maneuver, using in this case stimulation as the reference technique. Such an exercise is justified in that forced inhalation is employed as a reference technique in pathophysiology laboratories solely because it became widely used earlier. However, magnetic stimulation might, in theory, be a more suitable reference method because it does not require the cooperation of the subject and so has methodological advantages. Thus, when Pdi_{sniff} was assessed with regard to muscle weakness as established by Pdi_{twitch} , the overall results (predictive power and error in the prediction) were equivalent to the reference technique, something implicit in a reciprocal evaluation of 2 techniques. However, Pdi_{sniff} had a notably lower sensitivity and specificity, leading to false negatives, with the corresponding serious consequences in the management of the patients.

We conclude that the magnetic cervical stimulation technique is a good alternative to sniff maneuvers in clinical practice. The main advantage of the technique is its high sensitivity, but this is achieved at the expense of a high number of patients falsely diagnosed with muscle weakness. This technique is of particular interest in patients with difficulties understanding instructions or in a critical condition when the main aim is to rule out diaphragmatic dysfunction.

Acknowledgments

The authors thank Àngela Roig, Nuria Soler, and Miriam Artiaga for their collaboration in the functional assessment of the patients.

REFERENCES

- 1. Global Initiative for Chronic Obstructive Lung Disease. NHLBI/WHO. Available from: www.goldcopd.com
- Siafakas NM, Vermeire P, Priede NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and manegement of chronic obstructive pulmonary disease (COPD). ERS consensus statement. Eur Respir J. 1995;8:1398-420.
- American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1995;152:S77-S120.
- Barbera JA, Peces-Barba G, Agustí AG, Izquierdo JL, Monsó E, Montemayor T, et al. Guía clínica para el diagnóstico y tratamiento de la enfermedad pulmonar obstructiva crónica. Arch Bronconeumol. 2001;37:297-316.
- 5. Gea J, Barreiro E, Orozco-Levi M. Oxidative stress, cytokines and respiratory muscle dysfunction. Clin Pulm Med. In press 2006.
- American Thoracic Society and European Respiratory Society. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. Am J Resp Crit Care Med. 1999;159 Suppl:1-40.
- Gea J, Orozco-Levi M, Barreiro E, Ferrer A, Broquetas JM. Structural and functional changes in the skeletal muscles of COPD patients: the "compartments" theory. Mon Arch Chest Dis. 2001;56:214-24.
- 8. Agustí AG, Noguera A, Sauleda J, Miralles C, Batle S, Busquets X. Systemic inflammation in chronic respiratory diseases. European Respiratory Monograph. 2003;8;46-55.
- Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers. Am J Respir Crit Care Med. 1996;154:1055-60.
- Sauleda J, García-Palmer FJ, González G, Palou A, Agustí AG. The activity of cytochrome oxidase is increased in circulating lymphocytes of patients with chronic obstructive pulmonary disease, asthma, and chronic arthritis. Am J Respir Crit Care Med. 2000;161:32-5.
- 11. Noguera A, Busquets X, Sauleda J, Villaverde JM, MacNee W, Agustí AG. Expression of adhesion molecules and G proteins in circulating neutrophils in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;158:1664-8.
- Mathur R, Cox IJ, Oatridge A, Shephard DT, Shaw RJ, Taylor-Robinson SD. Cerebral bioenergetics in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;160:1994-9.
- 13. Sharkey RA, Mulloy EM, Kilgallen IA, O'Neill SJ. Renal functional reserve in patients with severe chronic obstructive pulmonary disease. Thorax. 1997;52:411-5.

MARTÍNEZ-LLORENS J ET AL. DETERMINATION OF MAXIMAL DIAPHRAGM STRENGTH IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: CERVICAL MAGNETIC STIMULATION VERSUS TRADITIONAL SNIFF MANEUVER

- 14. Napal J, Cuerno Y, Olmos JM, Riancho JA, Amado JA, González Macías J. Cambios en la masa ósea de pacientes con cirrosis hepática, enfermedad pulmonar obstructiva crónica, diabetes insulinodependiente e hiperparatiroidismo primario. Med Clin (Barc). 1993;100:576-9.
- 15. Marquis K, Debigare R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002;166:809-13.
- 16. Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. Chest. 2002;121 Suppl:127-30.
- Lótters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a metaanalysis. Eur Respir J. 2002;20:570-6.
- de Andrade AD, Silva TN, Vasconcelos H, Marcelino M, Rodrigues-Machado MG, Filho VC, et al. Inspiratory muscular activation during threshold (R) therapy in elderly healthy and patients with COPD. J Electromyogr Kinesiol. 2005;15:631-9.
- Aran X, Gea J, Guiu R, Aguar MC, Sauleda J, Broquetas JM. Comparación de tres maniobras diferentes para la obtención de la presión transdiafragmática máxima. Arch Bronconeumol. 1992;28:112-5.
- Laporta D, Grassino A. Assessment of transdiaphragmatic pressure in humans. J Appl Physiol. 1985;58:1469-76.
- 21. Gea J, Orozco-Levi M, Barreiro E, Ramírez-Sarmiento AL, Gáldiz JB, López de Santamaría E. Pruebas para el estudio de las enfermedades neuromusculares. Manual SEPAR de procedimientos. Módulo 4: Procedimientos de evaluación de la función pulmonar II. Barcelona: Luzaín; 2004. p. 125.
- 22. Similowski T, Fleury B, Launois S, Cathala HP, Bouche P, Derenne JP. Cervical magnetic stimulation: a new painless method for bilateral phrenic nerve stimulation in conscious humans. J Appl Physiol. 1989;67:1311-8.
- Gea J, Espadaler JM, Guiu R, Aran X, Seoane L, Broquetas JM. Diaphragmatic activity induced by cortical stimulation: surface versus esophageal electrodes. J Appl Physiol. 1993;74:655-8.
 Polkey MI, Kyroussis D, Keilty SE, Hamnegard CH, Mills GH,
- Polkey MI, Kyroussis D, Keilty SE, Hamnegard CH, Mills GH, Green M, et al. Exhaustive treadmill exercise does not reduce twitch transdiaphragmatic pressure in patients with COPD. Am J Respir Crit Care Med. 1995;152:959-64.
- Hamnegard CH, Wragg S, Kyroussis D, Mills GH, Polkey MI, Moran J, et al. Diaphragm fatigue following maximal ventilation in man. Eur Respir J. 1996;9:241-7.
- 26. Gáldiz JB, Bustamante V, Camino J, Cabriada V. Comparación de la presión en boca, *twitch*, tras estimulación magnética anterior frente a estimulación magnética posterior en sujetos sanos. Arch Bronconeumol. 2000;36:557-62.
- Hamnegard CH, Bake B, Moxham J, Polkey MI. Does undernutrition contribute to diaphragm weakness in patients with severe COPD? Clin Nutr. 2002;21:239-43.
- Hammegard CH, Wragg SD, Mills GH, Kyroussis D, Polkey MI, Bake B, et al. Clinical assessment of diaphragm strength by cervical magnetic stimulation of the phrenic nerves. Thorax. 1996;51:1239-42.
- el-Kabir DR, Polkey MI, Lyall RA, Williams AJ, Moxham J. The effect of treatment on diaphragm contractility in obstructive sleep apnea syndrome. Respir Med. 2003;97:1021-6.
- Roca J, Sanchis J, Agustí-Vidal A, Segarra F, Navajas D, Rodríguez-Roisin R, et al. Spirometric reference values from Mediterranean population. Bull Eur Physiopathol Respir. 1986;22:217-24.
- Roca J, Burgos F, Barberá JA, Sunyer J, Rodríguez-Roisín R, Castellsagué J, et al. Prediction equations for plethismografic lung volumes. Respir Med. 1998;92:454-60.

- Roca J, Rodríguez-Roisín R, Cobo E, Burgos F, Pérez J, Clausen JL. Single breath carbon monoxide diffusing capacity prediction from a Mediterranean population. Am Rev Respir Dis. 1990;141:1026-32.
- Morales P, Sanchis J, Cordero PJ, Dies JL. Presiones respiratorias estáticas en adultos. Valores de referencia para población caucásica mediterránea. Arch Bronconeumol. 1997;33:213-9.
- Luo YM, Hart N, Mustfa N, Man WD, Rafferty GF, Polkey MI, et al. Reproducibility of twitch and sniff transdiaphragmatic pressures. Respir Physiol Neurobiol. 2002;132:301-6.
- Rochester DF, Braun NMT, Arora NS. Respiratory muscle strength in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1979;119:151-4.
- Similowsky T, Yan S, Gauthier AP, Macklem PT. Contractile properties of the human diaphragm. N Engl J Med. 1991;325:917-23.
- Macklem PT, Macklem DM, de Troyer A. A model of inspiratory muscle mechanics. J Appl Physiol. 1983;55:547-57.
- Orozco-Levi M, Gea J. El diafragma. Arch Bronconeumol. 1997; 33:399-411.
- 39. Sánchez J, Medrano G, Debese B, Riquet M, Derene JP. Muscle fibre types in costal and crural diaphragm in normal men and in patients with moderate chronic respiratory disease. Bull Eur Physiopathol Respir. 1985;21:351-6.
- 40. Orozco-Levi M, Lloreta J, Minguella J, Serrano S, Broquetas JM, Gea J. Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164:1734-9.
- Lloreta J, Orozco-Levi M, Gea J, Corominas JM, Serrano S. Selective diaphragmatic mitochondrial abnormalities in sever airflow obstruction. Ultraestruct Pathol. 1996;20:67-71.
- 42. Barreiro E, de la Puente B, Minguella J, Corominas JM, Serrano S, Hussain SN, et al. Oxidative stress and respiratory muscle dysfunction in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171:1116-24.
- Orozco-Levi M, Gea J, Lloreta JL, Félez M, Minguella J, Serrano S, et al. Subcellular adaptation of the human diaphragm in chronic obstructive pulmonary disease. Eur Respir J. 1999;13:371-8.
- Levine S, Kaiser L, Leferovich J, Tikunov B. Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. N Engl J Med. 1997;337:1799-806.
- Hughes PD, Polkey MI, Kyroussis D, Hamnegard CH, Moxham J, Green M. Measurement of sniff nasal and diaphragm twitch mouth pressure in patients. Thorax. 1998;53:96-100.
- 46. Chieveley-Williams S, Dinner L, Puddicombe A, Field D, Lovell AT, Goldstone JC. Central venous and bladder pressure reflect transdiaphragmatic pressure during pressure support ventilation. Chest. 2002;121:533-8.
- Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Diaphragm strength in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1996;154:1310-7.
- Mills GH, Kyroussis D, Hamnegard CH, Polkey MI, Green M, Moxham J. Bilateral magnetic stimulation of the phrenic nerves from an anterolateral approach. Am J Respir Crit Care Med. 1996;154:1099-105.
- 49. Hopkinson NS, Man WD, Dayer MJ, Ross ET, Nickol AH, Hart N, et al. Acute effect of oral steroids on muscle function in chronic obstructive pulmonary disease. Eur Respir J. 2004;24:137-42.
- Hamnegard CH, Wragg SD, Mills GH, Kyroussis D, Polkey MI, Bake B, et al. Clinical assessment of diaphragm strength by cervical magnetic stimulation of the phrenic nerves. Thorax. 1996;51:1239-42.
- Luz Z, Tang X, Huang X. Phrenic nerve conduction and diaphragmatic motor evoked potentials: evaluation of respiratory dysfunction. Chin Med J. 1998;111:496-9.