Research Article

Explorations of Unilateral Diaphragmatic Paralysis

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Objective. The aim of the present study was to evaluate sniff test, maximal inspiratory pressure, and presence of paradoxical inspiratory diaphragmatic movements and their diagnostic value in patients referred for suspicion of diaphragmatic dysfunction. **Methods.** Twenty-two patients (8 men and 14 women, 58 ± 13 years) with suspected diaphragmatic dysfunction were included. Pulmonary function test was evaluated by spirometry. Diaphragm dysfunction was diagnosed with unilateral phrenic nerve stimulation. Esophageal pressure was recorded during sniff test and maximal static inspiratory movements. Detection of paradoxical diaphragmatic movement was performed with anteroposterior projection of chest X-ray fluoroscopic video. **Results.** Phrenic nerve stimulation enabled diagnosis of diaphragmatic paralysis in 15 of the 22 patients. The remaining 7 patients had normal explorations. Lung volumes were significantly lower in patients with diaphragmatic paralysis than in control subjects, as maximal inspiratory pressure. No patient with normal diaphragmatic exploration had paradoxical inspiratory movement. The combined diagnostic value of reduced esophageal pressure during sniff test, reduced esophageal pressure during maximal static inspiratory movements, and presence of paradoxical inspiratory movement had a sensitivity of 87% and a specificity of 71%. **Conclusion.** Our results suggest that, in most cases, a combination of sniff test, maximal inspiratory pressure, and paradoxical inspiratory movement could help to diagnose diaphragmatic dysfunction. Nevertheless, phrenic nerve stimulation remains the best test for assessing diaphragmatic dysfunction.

1. Introduction

Diaphragmatic paralysis is common and may be due to infectious, iatrogenic, or malignant causes, although the most common is *frigore* paralysis. Damage to the diaphragm or the phrenic nerve decreases inspiratory pressure, leading to diaphragmatic weakness and reduction in inspiratory muscle capacity [1] and lung volume, which in turn impair respiratory muscle endurance [2] and produce dyspnea [3]. Diaphragmatic dysfunction should thus be considered as a differential diagnosis of unexplained dyspnea, but its definitive diagnosis is difficult to assert. Definitive diagnosis can be obtained by phrenic nerve stimulation combined with measurement of twitch transdiaphragmatic pressure [4, 5], but the technique may be difficult in some patients. In clinical practice, suspicion of diaphragmatic paralysis is usually based

on diaphragmatic curve during diaphragmatic fluoroscopic examination [6], inspiratory muscle strength evaluated by sniff test and maximal inspiratory pressure, and phrenic nerve stimulation [7]. Nevertheless, the relative value of the different explorations, as well as their place in the diagnosis of diaphragmatic paralysis, has not yet been clearly established. Therefore, the aim of the present study was to evaluate their diagnostic value in patients with diaphragmatic paralysis diagnosed by phrenic nerve stimulation.

2. Methods

2.1. Patients. Twenty-two patients with suspicion of diaphragmatic dysfunction (8 men and 14 women, 58 ± 13 years) were retrospectively included in the study, from 2008 to 2012. Criteria for inclusion were suspicion of diaphragmatic

dysfunction due to phrenic nerve paralysis. The patients did not suffer from other muscular or neurologic disorders and had no contraindication to undergoing magnetic stimulation.

2.2. Measurements. Lung volume, spirometry, and flow-volume curves were measured according to standard guidelines and expressed as percentages of published values [8] (Master-Screen Body Plethysmograph, Carefusion, San Diego, CA).

After insertion of an esophageal balloon catheter and a gastric balloon catheter (70 cm long catheter; 1.4 mm external diameter; Marquat, Boissy Saint Léger, France), esophageal and gastric pressures [9] were measured in cmH_2O with differential pressure transducer (DA 100C, Biopac Systems Inc., Santa Barbara, CA) [10]. Sniff maneuvers were performed at end of expiration with the patient in seated position. Patients were asked to perform sharp and maximal sniff maneuvers until peak esophageal pressure no longer increased. Maneuvers were only retained if sniff inspiratory time was under 0.5 seconds. Maximum sniff efforts were encouraged verbally and patients performed three series of five to ten sniffs, separated by at least 30 seconds [10]. Maximal static inspiratory pressure was measured from functional residual capacity (FRC) while seated and wearing a nose clip. Maximum inspiratory efforts were also encouraged verbally. Three maneuvers were performed separated by at least 30-second rest and continued until no further increase in pressure could be obtained [11].

Sniff test was considered as pathological if under 70 cmH_2O for men and 60 cmH_2O for women [11–13]. Maximal static inspiratory pressure (MIF) was measured from FRC while seated and wearing a nose clip [14]. MIF was considered as pathological if under 80 cmH_2O for men and 70 cmH_2O for women [11, 13–15]. Sniff maneuvers and maximal inspiratory pressure were performed before phrenic nerve stimulations with a 10-minute delay to avoid potentiation [16]. Diaphragm stimulations were performed using magnetic stimulation as previously described [17]. Briefly, bilateral phrenic nerve magnetic stimulations were performed at end expiratory time using a Magstim 200 stimulator powering a 90 mm circular coil (2.5 Tesla maximal output) (Magstim Ltd., Whitland, UK). The coil was placed at C7 level and three supramaximal reproducible stimulations were retained. Unilateral magnetic phrenic nerve stimulations (right and left phrenic nerve stimulations) were performed with a 43 mm branding iron type figure eight coil (Magstim Ltd., Whitland, UK), according to the technique described by Mills et al. [18]. A diagnosis of unilateral diaphragmatic paralysis was defined as a decrease of under 10 cmH_2O in transdiaphragmatic pressure (Pdi) in response to unilateral phrenic nerve stimulation (ums) [13].

Anteroposterior projection fluoroscopic images were acquired with a radio amplifier (Flexiview 8800, General Electric, United Medical Technologies Corp., Fort Myers, FL) and recorded on a computer at 12 frames per second for later analysis (MMS, Tubingen, The Netherlands). Two sequences were recorded for each hemidiaphragm and two sequences were performed with the entire diaphragm in the field. The patients were in an upright position during testing and were

asked to perform sharp and strong sniffs as previously learned during sniff test. A paradoxical inspiratory movement was defined as an inspiratory elevation of one hemidiaphragm during normal movement of the other hemidiaphragm, that is, a descent during the sharp sniff [19].

2.3. Data Analysis. Esophageal pressure amplitudes were measured from baseline to peak. Maximal sniff esophageal pressures (Pes, sniff) and maximal static inspiratory pressure (Pes, mip) were retained for analysis. Maximal esophageal and gastric pressures induced by phrenic nerve cervical magnetic stimulation were measured to calculate transdiaphragmatic pressure (Pdi) during cervical magnetic stimulation (CMS) or unilateral cervical stimulation (UMS) (resp., Pdi, cms and Pdi, ums). Presence or absence of paradoxical diaphragmatic inspiratory movements was noted.

2.4. Statistics. Statistical analyses were performed using StatView 5.0 software (SAS Institute Inc.). All results are expressed as means $\pm$ standard error (SE). Differences between the two groups of patients were analyzed with nonparametric Mann-Whitney test and were considered significant when the probability P of a type I error was 0.05 or less. Sensitivity and specificity were calculated for each test, with diaphragmatic dysfunction being defined by a pathological Pdi measurement in response to unilateral phrenic nerve stimulation.

3. Results

The results of transdiaphragmatic pressure (Pdi) measurement in response to unilateral phrenic nerve stimulation enabled diagnosis of 15 diaphragmatic paralyses and 7 normal explorations. Ten of the 15 diaphragmatic paralyses had right diaphragmatic dysfunction and five had left diaphragmatic dysfunction. Vital capacity (VC), forced expiratory volume in one second (FEV1), FRC, Pes, mip, Pes, sniff, Pdi, ums, Pdi, cms, and videofluoroscopy results are summarized in Table 1.

3.1. Pulmonary Function Tests. Results are presented in Table 1. There was a significant difference between the two groups for FEV1 ($P = 0.01$) and VC ($P = 0.05$). FRC tended to be lower in patients with diaphragmatic paralysis, but difference was not statistically significant ($P = 0.1$).

3.2. Diaphragmatic Strength. Pes, sniff was not statistically lower in patients with diaphragmatic paralysis (resp., $82.1 \pm 6.8 \text{ cmH}_2\text{O}$ versus $69 \pm 4.9 \text{ cmH}_2\text{O}$, $P = 0.08$). Pes, mip and Pdi, cms were higher in patients with no diaphragmatic paralysis than in patients with diaphragmatic paralysis (resp., $84.0 \pm 9.5 \text{ cmH}_2\text{O}$ versus $66.1 \pm 4.3 \text{ cmH}_2\text{O}$, $P < 0.05$, and $28.1 \pm 2.4 \text{ cmH}_2\text{O}$ versus $13.1 \pm 1.5 \text{ cmH}_2\text{O}$, $P < 0.0001$ (Figure 1)). Two patients did not correctly perform the maneuver to obtain maximal inspiratory pressure. Pdi, ums was not different between right and left side in patients with normal explorations (right: $16.4 \pm 1.5 \text{ cmH}_2\text{O}$, left: $18.2 \pm 1.4 \text{ cmH}_2\text{O}$, $P = 0.11$). Pdi, ums was significantly lower in patients with diaphragmatic paralysis, for both sides (Figure 2). Sensitivity

TABLE 1: Results summary, according to diaphragmatic status, with on one side confirmed diaphragmatic paralysis, and on the other side normal diaphragm. *P* value was calculated using Mann-Whitney nonparametric test between these two groups, and was significant for all presented variables, except Pes, sniff.

	Age (years)	Paralysis side Left/right/no	VC (% pred)	FEV1 (% pred)	FRC (% pred)	Pes, sniff (cmH ₂ O)	Pes, mip (cmH ₂ O)	Pdi, cms (cmH ₂ O)	Pdi, ums (left) (cmH ₂ O)	Pdi, ums (right) (cmH ₂ O)	Paradox (y/n)
Patients with diaphragmatic paralysis											
#1	58	Right	28.5	25.1	#	42	32	8.0	6.0	5.0	y
#2	66	Right	84.4	76.8	72.8	71	47	13.0	12.0	4.0	y
#3	65	Right	100.0	100.0	100.0	54	69	10.6	7.4	4.0	y
#4	67	Right	34.1	40.5	83.5	53	70	5.0	10.0	4.0	y
#5	71	Right	71.3	60.5	143.8	60	44	10.0	5.0	0.0	n
#6	64	Right	57.3	58.9	54.0	57	61	3.0	6.0	3.0	y
#7	46	Left	106.6	93.8	88.8	100	85	13.0	8.0	20.0	n
#8	68	Right	88.8	61.7	64.8	48	#	6.0	8.0	4.0	y
#9	62	Left	85.1	86.0	68.2	65	69	18.0	9.0	19.0	n
#10	72	Left	115.8	117.3	93.5	110	82	20.0	6.0	6.0	n
#11	75	Right	106.7	89.7	95.0	71	63	20.0	11.0	8.0	n
#12	74	Right	92.5	75.3	109.5	72	72	17.7	9.6	7.1	n
#13	59	Left	70.7	75.9	50.1	70	74	18.0	4.0	5.0	y
#14	52	Right	79.6	80.2	67.4	71	89	13.0	6.0	8.0	y
#15	56	Left	73.0	70.1	178.8	91	69	21.0	8	8.0	n
Mean ± SE	63.7 ± 2.1		79.6 ± 6.5	74.1 ± 6.0	90.7 ± 9.4	69.0 ± 4.9	66.1 ± 4.3	13.1 ± 1.5	7.7 ± 0.6	7.0 ± 1.4	
Patients without diaphragmatic paralysis											
#16	51	No	107.2	97.3	106.0	92	90	34.0	19.0	15.0	n
#17	38	No	95.5	90.0	104.2	75	75	32.0	18.3	19.9	n
#18	32	No	96.4	93.8	88.7	116	91	25.0	25.0	23.0	n
#19	74	No	92.3	95.8	98.0	67	53	23.0	13.0	12.0	n
#20	41	No	107.8	102.3	92.5	80	122	36.0	19.0	16.0	n
#21	42	No	99.3	100.0	114.1	84	#	29.0	18.0	13.0	n
#22	44	No	87.4	89.6	115.4	61	73	18.0	15.0	16.0	n
Mean ± SE	46.0 ± 5.1		98. ± 2.8	95.5 ± 1.8	102.7 ± 3.9	82.2 ± 6.8	84.0 ± 9.5	28.1 ± 2.4	18.2 ± 1.4	16.4 ± 1.5	
<i>P</i> value	<0.01		0.05	0.01	0.1	0.08	0.05	<0.01	<0.01	<0.01	

VC: vital capacity.
FEV1: forced expiratory volume in one second.
FRC: functional residual capacity.
Pes, sniff: esophageal pressure during strong sniff.
Pes, mip: maximal esophageal inspiratory pressure.
Pdi, cms: transdiaphragmatic pressure induced by cervical bilateral phrenic nerve magnetic stimulation.
Pdi, ums: transdiaphragmatic pressure induced by unilateral phrenic nerve magnetic stimulation.

FIGURE 1: Esophageal pressure, gastric pressure, and transdiaphragmatic pressure induced by cervical bilateral phrenic nerve magnetic stimulation (Pes, cms, Pgas, cms, and Pdi, cms). Distribution of values between patients with normal diaphragmatic explorations and patients with diaphragmatic paralysis, expressed in cmH₂O. Asterisk denotes significant difference ($P < 0.05$).

FIGURE 2: Esophageal pressure, gastric pressure, and transdiaphragmatic pressure induced by unilateral phrenic nerve magnetic stimulation (Pes, ums, Pgas, ums, and Pdi, ums). Distribution of values for each side, between patients with normal diaphragmatic explorations and patients with diaphragmatic paralysis, expressed in cmH₂O. For patients with diaphragmatic dysfunction, results are divided according to the side of the injury. Asterisk denotes significant difference with normal patients ($P < 0.05$).

and specificity were, respectively, 53% and 100% for Pes, sniff, 67% and 71% for Pes, mip, and 93% and 86% for Pdi, cms.

3.3. Diaphragmatic Movements. On diaphragm radiography, no patient with normal diaphragmatic exploration had paradoxical inspiratory movement. In patients with diaphragmatic paralysis, eight experienced paradoxical inspiratory

movement and seven normal diaphragmatic curve for the paralyzed hemidiaphragm. Sensitivity was therefore 53% and specificity 100%.

When Pes, sniff was abnormal, Pes, mip was abnormal and presence of a paradoxical inspiratory movement was noted; sensitivity was calculated at 87% and specificity at 71% for diaphragmatic dysfunction diagnosis.

4. Discussion

This study demonstrated that diaphragmatic paralysis induced respiratory muscle weakness and paradoxical inspiratory movements of the paralyzed hemidiaphragm in a majority of patients with good sensitivity. Nevertheless, phrenic nerve stimulation remains the gold standard method for diagnosis of diaphragmatic paralysis.

While numerous methods have been proposed for diagnosing diaphragmatic paralysis and diaphragmatic weakness, magnetic phrenic nerve stimulation [12], either unilateral [15] or bilateral [20, 21], is currently the most precise technique for diagnosing phrenic nerve paralysis [2, 12] or diaphragmatic weakness [12, 22]. The major difficulty in diaphragmatic explorations is that there are no cut-off values for clear separation of “normal” and “pathological” explorations. Hart et al. proposed a Pdi, ums of less than 3.5 cmH₂O [2]. This cut-off was arbitrarily chosen, and the authors acknowledged that, with such a low value, only severe diaphragm weakness would be diagnosed as “diaphragm paralysis.” Luo et al. investigated the value of Pdi, cms on normal subjects and found it to be 28 ± 5 cmH₂O [23]. From this study, Steier et al. [24] proposed as cut-off value 18 cmH₂O for Pdi, cms, but did not mention Pdi, ums. Recently, a review [13], proposed a cut-off value of 10 cmH₂O for Pdi, ums and 20 cmH₂O for Pdi, cms to diagnose clinically significant diaphragmatic weakness, which we decided to take into account. Differences in diaphragmatic strengths obtained after bilateral phrenic nerve stimulation compared to unilateral phrenic nerve stimulation observed in our study have been previously described and can be explained by the stabilizing effect of cervical magnetic stimulations on the rib cage [25]. It should be noted that the relatively low number of patients included in the present study is due to the fact that inclusion criteria were difficult to achieve for many patients. In particular Pdi, cms and Pdi, ums were very often lacking, with patients not achieving test completion.

Our results confirm that mobilizable lung volumes are lower in cases of diaphragmatic dysfunction, in absence of any other pulmonary diseases. Consequently, pulmonary function tests are useful as a first approach and to ensure easily led follow-up of patients suffering from diaphragmatic dysfunction. Nevertheless, normal pulmonary function test is unable to rule out diaphragmatic dysfunction. In our study, Pes, sniff was the only test which allowed assessment of diaphragmatic dysfunction when abnormal with no false positive, but with subsequent false negatives [26]. It seems from the report that sniff transdiaphragmatic pressure can be higher than maximal static transdiaphragmatic pressure [27, 28], although conflicting results have been reported in controls [29] and in patients [30].

Diaphragmatic video fluoroscopy can provide dynamic information on diaphragmatic movement. A study performed on inspiratory-expiratory radiographs obtained from 350 subjects aged between 30 and 80 years, during quiet tidal breathing in an erect position, and without evidence of respiratory disease, found mean tidal excursions of the domes of the right and left hemidiaphragms to be 3.3 and 3.5 cm, respectively [31]. Tidal diaphragmatic movement was on average 0.5 cm lower in women than in men. Despite similar mean values, unequal movement of the two hemidiaphragmatic domes in an individual subject is common, most commonly greater on the right [32, 33]. Unilateral diaphragm paralysis is easier to detect because there is paradoxical motion during tidal inspiration, with ascent of the paralyzed dome, contrasting with descent of the normal hemidiaphragm; this contrast can be amplified by sniff test, which induces a vigorous, short contraction in the normal hemidiaphragm [34]. In our study, paradoxical motion, such as Pes, Sniff, has excellent specificity, but lower sensitivity. Its presence can enable assessment of the existence of diaphragmatic dysfunction, but this exploration can be proved wrong for moderate dysfunction of a hemidiaphragm, or on the contrary for severe bilateral paralysis.

As seen above, no one single exploration (Pes, sniff, Pes, mip, search for paradoxical motion during sniff manoeuvre) is relevant in the diagnosis of diaphragmatic dysfunction, due to numerous false negatives, except Pdi, ums or Pdi cms measurements. Nevertheless, combining Pes, sniff, Pes, mip and paradoxical motion allows obtention of high sensitivity, at 87%. Consequently, a combination of easily performed, noninvasive explorations, confronted with clinical context, is very useful. Phrenic nerve stimulation should therefore be used for uncommon cases, when clinical argument is insufficient for diagnosis of diaphragmatic weakness, or when it is necessary to give the precise level of diaphragmatic paralysis.

In conclusion, our results suggest that, in most cases, combining Pes, sniff, Pes, mip measurements and diaphragmatic videofluoroscopy in search of an eventual paradoxical inspiratory diaphragmatic movement during sniff maneuvers is useful to manage suspicion of diaphragmatic dysfunction. However, phrenic nerve stimulation remains the best exploration to confirm diagnosis.

Disclosure

Neither funding nor grants nor equipment was provided for the project by any source; there was no financial profit for the authors. There has been no previous presentation of the research, paper, or abstract in any form.

Conflict of Interests

The authors declare that there is no conflict of interests.

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