Spontaneous recovery of diaphragmatic strength in unilateral diaphragmatic paralysis

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KEYWORDS
Sniff test;
Cervical magnetic stimulation;
Diaphragmatic paralysis

Summary The aim of the present study was to evaluate diaphragmatic strength in patients with unilateral diaphragmatic paralysis and to determine whether patients with recent diaphragm paralysis develop lower inspiratory pressure than patients with longstanding diaphragmatic paralysis. Twenty patients (16 men and 4 women, 62±12 years) and six control subjects were included (4 men and 2 women, 53±15 years) in the study. Esophageal pressure during sharp sniff (Pes,sniff), bilateral cervical phrenic nerve magnetic stimulation (Pes,cms) and unilateral phrenic nerve stimulation (Pes,ums) (in nine patients) were measured. Sixteen patients presented right diaphragmatic paralysis and four, left diaphragmatic paralysis. Pes,sniff was higher in control subjects than in patients with diaphragmatic paralysis (respectively 110±22 cmH\textsubscript{2}O and 82±24 cmH\textsubscript{2}O, \(P<0.05\)). There was no difference in Pes,cms between patients with diaphragmatic paralysis and control subjects (14±7 cmH\textsubscript{2}O vs. 16±4 cmH\textsubscript{2}O; ns). Pes,ums after stimulation of the affected phrenic nerve was less than 4 cmH\textsubscript{2}O, was 8±2 cmH\textsubscript{2}O after stimulation of the intact phrenic nerve and was correlated to Pes,cms (\(R=0.87\), \(P<0.01\)). There was a positive correlation between Pes,cms, Pes,ums of the intact hemidiaphragm, Pes,sniff and the time from the onset of symptoms and the diaphragmatic explorations (respectively \(R=0.86\), \(P<0.0001\); \(R=0.72\), \(P<0.05\); \(R=0.48\), \(P<0.05\)). In conclusion, diaphragmatic strength after unilateral diaphragmatic paralysis seems to improve with time.

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Introduction

Damage to the phrenic nerves leads to diaphragmatic paralysis, which decreases inspiratory
pressure, leading to diaphragmatic weakness and a reduction in inspiratory muscle capacity\(^1\) and lung volume, which in turn impairs respiratory muscle endurance\(^2\) and produces exertional dyspnea.\(^3\) However, most patients with unilateral paralysis are able to maintain adequate ventilation and gas exchange at rest and during mild exercise, probably through compensatory mechanisms such as an increase in motor output to the intercostal muscles and the normal hemidiaphragm.\(^3\)

Nevertheless, a modification of the structure of the paralyzed hemidiaphragm should result in a compensatory increase in the diaphragmatic strength of the intact hemidiaphragm. On the one hand, diaphragmatic denervation causes muscle fibrosis, fiber atrophy and necrosis,\(^4\)–\(^6\) which should impair mobility of the paralyzed hemidiaphragm. On the other hand, in unilateral diaphragmatic paralysis, diaphragmatic strength is largely determined by the balance between the force generated by the change in pleural pressure and the force generated by the intact hemidiaphragm.\(^7\) A modification of the ultrastructure of the inactive hemidiaphragm as fibrosis should thus limit paradoxical movements and theoretically improve the diaphragmatic strength of the intact hemidiaphragm over the time.

The aim of the present study was thus to evaluate diaphragmatic strength in patients with unilateral diaphragmatic paralysis using the sniff test and inspiratory pressure induced by phrenic nerve stimulation and to determine whether patients with recent diaphragmatic paralysis are more likely to develop lower inspiratory pressure than those with longstanding diaphragmatic paralysis.

**Methods**

**Patients**

Twenty patients (16 men and 4 women, 62 ± 12 years) were consecutively included in the study. The criteria for inclusion were (1) the presence of unilateral phrenic nerve paralysis diagnosed by paradoxical inspiratory hemi-diaphragmatic movements detected by chest fluoroscopic examinations\(^8\) or chest X-ray associated with an increase in phrenic nerve conduction time or absence of diaphragmatic compound muscle action potential (CMAP)\(^9,10\) in response to phrenic nerve stimulation, (2) no other muscular or neurological disorder and (3) the absence of bronchial obstruction detected by pulmonary function test. In all cases, the diaphragmatic paralysis was unilateral and peripheral (thoracic or neck surgery, cervical arthrosis or of unknown etiology). No patients presented neuralgic amyotrophy.

Six control subjects (4 men and 2 women, 53 ± 15 years) were also included based on normal pulmonary function tests, normal fluoroscopic evaluations, normal diaphragmatic explorations and no history of thoracic, muscular or neurological disease.

**Pulmonary function test**

Lung volume, spirometry and flow-volume curves were obtained for all patients except five (8,9,10,11,17) because of a lack of reproducibility. The measurements were performed according to standard guidelines\(^11\) and expressed as percentages of published values.\(^11\)

**Esophageal pressure**

Esophageal pressure was recorded using an esomometry perfused catheter system (150-cm-long catheter; 5 mm external diameter; Marquat, Boissy Saint Léger, France; pneumatic perfusion device, 15 ml/h, MIU, Strasbourg, France). The catheter was inserted into the nose and the lumen was placed in the distal esophagus to measure esophageal pressure as an indication of pleural pressure based on the occlusion test.\(^12\)

**Diaphragm electromyograms (EMG)**

Diaphragm EMGs were recorded bilaterally using two pairs of bipolar surface electrodes (Comepa, Saint Denis, France) positioned over the right and left hemidiaphragms on the midclavicular plane\(^13\) and recorded using an electromyogram amplifier (EMG 100C, Biopac Systems Inc., Santa Barbara, CA, USA).

Pressures and EMGs were recorded using an MP 150 acquisition system (Biopac). After amplification, the signals were continuously recorded at a rate of 1 kHz for pressure and 50 kHz for EMGs (2–20 kHz band-pass filtering).

**Sniff test**

Sniff maneuvers were performed with the subject seated, at end expiration. The patients were asked to performed sharp and maximal sniff maneuvers until the peak esophageal pressure no longer increased. Sniffs were only retained if sniff inspiratory time was under 0.5 s. Maximum sniff efforts were encouraged verbally and subjects performed three series of ten sniffs, separated by at least 30 s.\(^14\)
Bilateral phrenic nerve stimulation

Sniff maneuvers were performed before phrenic nerve stimulations with a 30 min delay to avoid potentiation. 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 the C7 level and three supramaximal reproducible stimulations were retained.

Additional experiments

In nine patients, unilateral magnetic phrenic nerve stimulations (right and left phrenic nerve stimulations) were performed with a 43 mm branding iron type figure eight coil (Magstim), according to the technique described by Mills et al.

Data analysis

Esophageal pressure amplitudes were measured from baseline to peak. Maximal sniff esophageal pressures (Pes,sniff) and maximal esophageal pressures induced by bilateral phrenic nerve cervical magnetic stimulation (Pes,cms) or unilateral phrenic nerve stimulation (Pes,ums) were retained for analysis. During the bilateral phrenic nerve stimulations, right and left phrenic nerve conduction times were measured from the stimulation artifact to the beginning of the CMAP.

Statistics

Statistical analyses were performed using Statview 5.0 software (SAS Institute, Berkeley, CA, USA) running on a G4 Macintosh computer. All results are expressed as means ± standard error (SE). Statistical associations were studied using the z-test for correlation (R and P). Differences between the groups of patients were analyzed using an analysis of variance (Fisher test) and were considered significant when the probability p of a type I error was 0.05 or less.

Results

Sixteen patients presented a right diaphragmatic paralysis and four, a left diaphragmatic paralysis. Lung function data, the results of bilateral phrenic nerve stimulations and sniff tests, age and sex are presented in Table 1. The median time from the onset of symptoms to the respiratory muscle strength tests was 14 months (1–48 months). One patient presented a right phrenic nerve paralysis associated with bilateral vocal cord paralysis in adduction, which explained the reduction in forced expiratory volume at first second (FEV₁).

Diagnosis of diaphragmatic paralysis

All patients from the control group presented a bilateral diaphragmatic CMAP after cervical phrenic nerve stimulation, with right and left phrenic nerve conduction times < 6.5 ms. All patients with phrenic nerve paralysis presented a paradoxical inspiratory ascension of the paralyzed hemidiaphragm during fluoroscopic examination or chest X-ray. After bilateral phrenic nerve stimulation, six patients presented no unilateral CMAP and 14 patients presented a unilateral increase in phrenic nerve conduction time compared to the intact hemidiaphragm and to control subjects (respectively 7.8 ± 0.6, 6.0 ± 0.5 and 5.9 ± 0.6 ms, P < 0.0001).

Pulmonary function tests

VC, FEV₁ and FRC values are presented in Table 1. They were lower in patients with diaphragmatic paralysis than in control subjects (respectively, 76 ± 22% vs. 111 ± 18%, P < 0.01; 73 ± 27% vs. 110 ± 18%, P < 0.01 and 80 ± 18% vs. 101 ± 20%, P < 0.05). There was no difference in FEV₁/VC between the two groups (92 ± 19% vs. 101 ± 6%).

Diaphragmatic strength

Pes,sniff was higher in control subjects than in patients with diaphragmatic paralysis (respectively 110 ± 22 cmH₂O and 83 ± 24 cmH₂O; P < 0.05) (Fig. 1A). There was no difference in Pes,cms between patients with diaphragmatic paralysis and control subjects (14 ± 7 cmH₂O vs. 16 ± 4 cmH₂O; ns) (Fig. 1B). Eleven patients with unilateral phrenic nerve paralysis had a Pes,cms > 10 cmH₂O. There was no correlation between Pes,cms and Pes,sniff (R = 0.37, ns).

Among patients with diaphragmatic paralysis, Pes,ums was under 4 cmH₂O after stimulation of the affected phrenic nerve, was 8 ± 2 cmH₂O after stimulation of the intact phrenic nerve which was correlated with Pes,cms (R = 0.87, P < 0.01).

There was no difference between patients with right or left phrenic nerve paralysis (respectively, sniff test: 83 ± 6 cmH₂O vs. 80 ± 9 cmH₂O, ns;
**Table 1** Clinical presentation, pulmonary function tests and diaphragmatic exploration results.

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Pes,sniff: esophageal pressure measured during sniff; Pes,cms: esophageal pressure measured during bilateral phrenic nerve stimulation; Pes,ums: esophageal pressure measured during stimulation of the intact phrenic nerve; R PNCT: right phrenic nerve conduction time; L PNCT: left phrenic nerve conduction time; Delay: interval from the onset of clinical symptoms to the diaphragmatic explorations; Clin: diaphragmatic paralysis (DP) and control subjects (C).
Evolution of diaphragmatic strength from the onset of symptoms to the diaphragmatic explorations

There was a positive correlation between Pes,cms, Pes,ums of the intact hemidiaphragm, Pes,sniff and the time from the onset of symptoms to the
diaphragmatic explorations (respectively $R = 0.86$, $P < 0.0001$; $R = 0.72$, $P < 0.05$; $R = 0.48$, $P < 0.05$) (Fig. 2). The pulmonary function tests did not correlate over time from the onset of symptoms to the diaphragm explorations (VC: $R = 0.100$, ns; FEV$_1$: $R = 0.123$, ns; FRC: $R = 0.001$, ns).

The linear regression demonstrated that Pes,cms was greater than $10\,\text{cmH}_2\text{O}$ when the time from the onset of clinical symptoms to the diaphragmatic explorations exceeded approximately 1 year.

Discussion

This study demonstrated that in patients with unilateral diaphragmatic paralysis, respiratory muscles and diaphragmatic strength improve with time and was close to normal in patients with longstanding one. In addition, in these patients, diaphragmatic strength depended essentially of intact hemidiaphragm.

Critiques of the method

The patients included in our study were consecutive patients with isolated unilateral phrenic nerve paralysis and no other neurological or muscular disease. While numerous methods have been proposed for diagnosing diaphragmatic paralysis and diaphragmatic weakness, magnetic phrenic nerve stimulation, either unilateral or bilateral, is currently the most precise technique for diagnosing phrenic nerve paralysis or diaphragmatic weakness. Normal phrenic nerve conduction times were under $6.5\,\text{ms}$, which is in accordance with previously published results based on cervical magnetic stimulation of phrenic nerves. These studies demonstrated that, with this technique, right and left phrenic nerve conduction times were always under $6.5\,\text{ms}$ in normal subjects and shorter than those obtained with electrical stimulation or unilateral magnetic stimulation of phrenic nerves in the neck. We are thus confident that patients who presented an increase in phrenic nerve conduction time had diaphragmatic paralysis. We did not analyze the amplitude of the CMAP because there is no normal value in the literature and because there is too much subject- and electrode-dependent variability with surface electrodes. The surface electrodes were positioned at the best site for recording diaphragmatic and uncontaminated CMAP or motor-evoked potentials.

We recorded esophageal pressure as a measure of diaphragmatic muscular strength. The measurement of esophageal pressure alone in response to phrenic nerve stimulation provides an intermediate approach between the measurement of transdiaphragmatic pressure and mouth pressure. While twitch esophageal pressure measurements eliminate the problem of incomplete pressure equilibration due to glottic closure or airway time constant, they are more complex to perform than twitch mouth pressure measurements. Esophageal pressure reflects overall inspiratory muscle effort and is not specific to diaphragm activation during voluntary maneuvers. However, esophageal pressure is strongly correlated with trans-diaphragmatic pressure in healthy subjects during phrenic nerve stimulation and is therefore a strong index of diaphragm activation.

Significance of the findings

Respiratory muscle strength

Inspiratory muscle strength is commonly evaluated by sniff maneuvers or static inspiratory efforts. We demonstrated that patients with unilateral phrenic nerve paralysis had a decrease in Pes,sniff compared to control group, which could be partly explained by the modification of geometrical configuration of the hemi-diaphragms induced by phrenic nerve paralysis. In dog with phrenic nerve paralysis, this sequential movement is largely determined by the balance between the force generated by pleural pressure and the force generated by the intact hemi-diaphragm and could alter diaphragmatic strength. In our study, it could be supposed that phrenic nerve paralysis or phrenic nerve paresis might have induced differences in respiratory muscle strength, changed the configuration of intact hemi-diaphragms, and altered Pes,sniff.

Regarding our patients with phrenic nerve paralysis, we failed to demonstrate a reduction in diaphragmatic strength compared to control group. Nevertheless, the lower value of Pes,cms in patients with recent unilateral diaphragmatic paralysis, which improves with time, suggests a recuperation of diaphragmatic strength with time.

Mechanism of respiratory muscle function recovery

In our study, we observed that patients with longstanding diaphragmatic paralysis had higher diaphragmatic strength than those with recent diaphragmatic paralysis. The rise in Pes,sniff and Pes, cms over time in our patients indicated that respiratory and diaphragmatic muscular strength might improve. This could be explained by
respiratory muscle adaptation and improvement of diaphragmatic function with time, by reinnervation of the diaphragm or muscular modification of the diaphragm.

It is already admitted that in patient with phrenic nerve paralysis, Pes,sniff may underestimate diaphragmatic muscle dysfunction. For example, it has been reported that patients with complete and bilateral phrenic nerve paralysis are able to generate a Pes,sniff of >30 cmH₂O mainly due to the inspiratory activity of the rib cage and neck muscles. It could be supposed in patients that diaphragmatic dysfunction increase respiratory drive to accessory respiratory muscle, to increase inspiratory depression. Those adaptive mechanisms might increase with time, explaining the correlation between Pes,sniff and time.

On the other hand, we also demonstrated a recuperation of diaphragmatic strength with time, which could be explained by diaphragmatic reinnervation or modification of diaphragmatic structure. Partial denervation or spontaneous reinnervation through the phrenic nerve should be considered since the stimulation of the altered phrenic nerve evoked a compound muscle action potential in 15 patients, with an increase in phrenic nerve conduction time. The motoneuron has a strong ability to regenerate after injury. However, the problems of nerve cell survival after a proximal axotomy, difficulty in axonal elongation and the lack of target specificity during nerve fibre re-growth interfere with a good functional restitution. Those adaptive mechanisms might increase with time, explaining the correlation between Pes,sniff and time.

In 1986, Brouillette et al. already described spontaneous diaphragmatic reinnervation in a 16-month-old infant who presented bilateral diaphragmatic paralysis and respiratory failure after removal of a thoracic teratoma, after end-to-end anastomosis of a transected phrenic nerve. Functional diaphragmatic reinnervation could also occur from the accessory phrenic nerve, which is described in human with a frequency around 86%. The responsibility of accessory phrenic nerve in functional diaphragmatic reinnervation has been evoked and suspected when cervical phrenectomy was one of different treatment of tuberculosis infection. In large series, it was incriminated to explain the persistence hemi diaphragmatic movements after unilateral cervical phrenectomy, and could therefore explain functional diaphragmatic reinnervation in unilateral phrenic nerve paralysis. Two other hypotheses could also be suggested: (1) spontaneous reinnervation by intercostal nerves, (2) cross innervation. Spontaneous reinnervation by intercostal nerves or cross innervation of the diaphragm remain a subject of controversy, and has been studied in animals in which results differ between authors and between animal species. In the rabbit, Rikard-Bell and Bystrzycka did not observe any contralateral retrograde labelling in the cervical spine. Marie et al. reported the same conclusion with functional tests. In contrast, in cats, spontaneous diaphragmatic reinnervation from left phrenic nerve has been reported but not confirmed. This phenomena has also been reported in rats and monkeys. However, in the patients where an unilateral phrenic nerve stimulation was performed, we did not observe a rise in Pes,ums after phrenic nerve stimulation of the paralyzed hemidiaphragm, indicating that there was probably no diaphragmatic reinnervation.

Modification of muscular histomorphometric parameters of the paralyzed hemidiaphragm, could also explain our results. Signs of denervation of the hemidiaphragm after phrenic nerve section could be seen in animals, including modifications of fiber size, fiber shape (angulated or rounded fibers), nuclear internalisations, apparition of fiber atrophy and necrotic fibers. These histological modifications in turn could decrease hemidiaphragm mobility and paradoxical movements and could increase the strength of the intact hemidiaphragm.

In conclusion, in patients with unilateral diaphragmatic paralysis, diaphragmatic and respiratory muscles strength is for improvement over time, with some recovery of diaphragmatic strength in the most patients.

References
Diaphragmatic strength in unilateral diaphragmatic paralysis 1951


