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Functional recovery of diaphragm paralysis: A long-term follow-up study

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Summary
Background: Long-term functional outcome of diaphragm paralysis is largely unknown.
Methods: A retrospective study was conducted in 23 consecutive patients (21 males, 56 ± 9 years) with uni- or bilateral diaphragm paralysis to examine whether functional respiratory recovery can be predicted from the compound motor action potential (CMAP) of the diaphragm at the time of diagnosis. Pulmonary function and CMAP were evaluated at baseline and at follow-up. CMAP amplitude and latency were recorded by surface electromyography with percutaneous electrical stimulation of the phrenic nerve. Patients were followed for (median) 15 months up to 131 months (range 5–131). Functional respiratory recovery was defined as an increase in forced vital capacity >400 ml.
Results: Functional recovery occurred in 43% of the patients after 12 months (10 out of 23) and in 52% after 24 months (12 out of 23). Type and etiology of paralysis did not influence recovery. CMAP, anthropometric characteristics and baseline pulmonary function did not predict functional respiratory recovery. Whether respiratory muscle training improved pulmonary function is uncertain. Moreover, it did not result in a greater percentage functional respiratory recovery. Relapse after an initial improvement was observed in 26% of the patients.
Conclusions: The present study indicates that functional recovery of diaphragm paralysis is difficult to predict and may occur years after the onset of the paralysis.

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Introduction

Interruption of the integrity of the phrenic nerve results in dysfunction of the ipsilateral hemidiaphragm, whereas bilateral diaphragm paralysis or paresis requires either lesion of both phrenic nerves or of the central nervous system. Typical causes of uni- and bilateral diaphragm paralysis or paresis include neuromuscular diseases[1,2] or isolated phrenic nerve conduction abnormality due to trauma, and inadvertent interruption of the phrenic nerve during surgical procedures in the neck[3] or thorax.[4] In most cases of diaphragm paralysis, the etiology remains unknown and paralysis is unilateral.[5–7]

Nerve conduction study of the phrenic nerve is useful in diagnosing a neuromuscular disease involving the diaphragm. Indeed, the compound motor action potential (CMAP) of the diaphragm is often reduced in amplitude in patients with diaphragm weakness compared with healthy subjects.[8,9] If the phrenic nerve lesion is complete, no diaphragm action potential is obtained after phrenic nerve stimulation.[4] Because the function of the diaphragm is dependent on phrenic nerve integrity, it can be speculated that severe or complete phrenic nerve damage may be associated with a poor prognosis for recovery. Hence, a phrenic nerve conduction study performed at the onset of symptoms may be a predictor of diaphragm functional recovery (FR). Indeed, in contrast to imaging techniques and ultrasound, it assesses the functionality of the diaphragm. In contrast to fluoroscopy, it can be used in any environment including the intensive care unit. Similarly, magnetic stimulation was not used in the present study because this technique was not available in our department as a routine technique 11 years ago. Still today, electrical nerve stimulation is more widely available in clinical routine. Further, this technique is still not used in our center to stimulate the phrenic nerves especially in an ICU environment where magnetic field may interfere with proper function of monitoring equipment used for the patient. Finally, because electrical stimulation is a widely used technique implemented in most hospitals as a routine technique, we speculated that it could have been a promising tool for prognosis of recovery from diaphragm paralysis. Importantly, in the present study, this technique was used during the whole duration of the study and the same investigator performed the test.

On the other hand, since vital capacity (and related forced vital capacity (FVC)) is influenced by the ability of all inspiratory muscles to generate a change in volume, measurements of vital capacity may be a useful tool to follow functional respiratory recovery in patients with diaphragm paralysis. This simple and accessible parameter is, indeed, used as a standard in clinical practice, especially because the fall in vital capacity from upright to supine position may be used to delineate respiratory from other pathology. As such, patients with diaphragmatic paralysis show substantial fall in vital capacity on lying down[10] and this has been advocated as a clinical test for diaphragm weakness.[11] Thus, in the context of absence of concomitant pulmonary disease, any improvement in vital capacity may be attributed to an improvement in respiratory muscle function. In the present study, vital capacity values were used as a simple tool to follow functional respiratory recovery in patients with diaphragm paralysis.

The prognosis for recovery from diaphragm paralysis is difficult to determine. The available studies are mostly case reports or include small numbers of patient (generally <15).[7,12–19] Follow-up of the patients is generally shorter than 4 years.[12–14,16–19] Recovery (usually detected by diaphragm CMAP, ultrasound, fluoroscopy, chest X-ray or transdiaphragmatic pressure) may occur months after onset of the paralysis[12,13,16–19] while in other cases, phrenic nerve injury appears irreversible.[14] The time course of recovery of the phrenic nerve is also depending on the type of injury and the distance over which regeneration occurs.[19] Because clinicians need better prediction of long-term functional respiratory recovery after uni- and bilateral diaphragm paralysis to base their clinical decision making on regarding treatment options and to inform patients on the anticipated outcome of their disease, we retrospectively analyzed all patients referred to our center in the past 11 years. The aim was to evaluate recovery rate of uni- and bilateral paralysis and to determine whether functional respiratory recovery based on FVC measurements could be predicted by different variables including a phrenic nerve conduction study and pulmonary function.

Methods

Population

The 23 patients (21 males; mean age, 56 ± 9 years; height, 173 ± 8 cm; body mass index, $28 \pm 5\,kg\,m^{-2}$) included in this study were referred to the pulmonary outpatient clinic of our university hospital between August 1994 and June 2005 for dyspnea. The referral source was chest physicians for 14 patients and general practitioners for the remaining nine patients. The patients included in the present study were in fact patients referred to our center for whom an electromyographic examination was asked by the consulted chest physician (MD). The diagnosis of unilateral (left side: $n = 5$; right side: $n = 11$) or bilateral ($n = 7$) diaphragm paralysis was confirmed after clinical and functional examination (pulmonary function, diaphragm electromyography or chest radiography). Seven patients came to the clinic within 1 week after the onset of their complaint, eight came between 2 and 4 months and seven came more than 5 months after the probable onset of the disease, while no information was available for one patient. The ethics committee of the University Hospitals Leuven granted approval for this retrospective study.

Design

Baseline phrenic nerve conduction studies were performed within 2 days after baseline pulmonary function tests. Patients were subsequently followed up at the discretion of the treating chest physician or until June 2005. Functional respiratory recovery was defined as an improvement in FVC (ΔFVC) greater than 400 ml. This value was chosen as more than twice the FVC reproducibility error range (150 ml).[20] If patients recovered, the FVC at the time of recovery was used as the recovery follow-up measure and patients were

included in the FR group. If patients did not recover, they were included in the non-functional recovery (NFR) group and the last available FVC was chosen as the follow-up assessment. At recovery follow-up time, maximal mouth pressures were measured in 19 patients and phrenic nerve conduction in six patients. During follow-up, 21 patients performed inspiratory resistive muscle training. Training modalities were adapted for each patient and consisted of a daily 30 min session of resistive breathing performed against an inspiratory resistance (40% of maximal inspiratory pressure, $P_{I\,max}$).

Pulmonary function tests

Spirometry (Sensor Medics 6200, Bilthoven, The Netherlands) was performed in the sitting position[21] in all patients and also in the supine position in most patients ($n = 15$). The best forced expiratory volume in 1 s (FEV_1) and FVC of at least three reproducible efforts for each position were expressed as a percentage of the predicted values.[21] Total lung capacity (TLC) and functional residual capacity (FRC) were also assessed according to the ERS guidelines for pulmonary function testing.[19]

Maximal expiratory mouth pressure ($P_{E\,max}$) was measured at TLC and $P_{I\,max}$ at residual volume according to the modified method of Black and Hyatt.[22] For this purpose, a rigid tube with a standardized leak was placed against the mouth to measure inspiratory and expiratory pressures using an electronic pressure transducer. Both maximal mouth pressures were determined as pressures that could be sustained for at least 1 s. Maximal verbal encouragement was given. Tests were repeated until variability among the three best attempts was less than 5%. The best value was reported and expressed as percentage of the predicted value.[23]

Phrenic nerve study

Phrenic nerve conduction was measured according to the technique described by Bolton's group.[8] Each phrenic nerve was stimulated sequentially at the posterior border of the sternocleidomastoid muscle in the supraclavicular fossa, just above the clavicle. A square-wave electrical pulse of 0.1 ms was delivered by a handheld felt-tipped bipolar stimulating electrode, connected to an electromyographic system (Medelec Synergy, Surrey, United Kingdom). After locating the phrenic nerve, stimulus intensity was increased until the maximal CMAP amplitude was obtained. Electrical phrenic nerve stimulation was further increased by another 20% to ensure supramaximality. The CMAP was recorded bipolarly with two surface electrodes (silver cup electrodes filled with conductive paste and taped to the skin). As described by Bolton,[24] the active electrode was located 5 cm above the tip of the xiphoid process and the reference electrode was placed 16 cm from the active electrode at the costal margin (level of the seventh intercostal space). A ground electrode was placed on the manubrium sterni. For each patient, stimulations were repeated until three reproducible CMAPs were obtained except when the CMAP was of low amplitude (100 μV or less), then five reproducible CMAPs were collected. CMAP amplitude and latency were measured using standard procedure. For CMAP latency, conduction time was measured from the stimulus artefact to the beginning of the (negative) deflection of the CMAP signal. For statistical analysis, CMAP values in patients with unilateral diaphragm paralysis were the values recorded on the affected side, whereas in patients with bilateral diaphragm paralysis the mean CMAP value of both sides was taken. An abnormal diaphragmatic response was defined as a CMAP amplitude below 300 μV and a CMAP latency higher than 8.1 ms which is in the range of previously reported limit.[8]

Statistical analysis

The differences between two groups of patients (uni- vs. bilateral, or FR vs. functionally non-recovery) were assessed with unpaired Student's *t*-test or Mann–Whitney *U*-test according to data distribution. Differences between the three etiologic groups (idiopathic, neurologic, etc.) were assessed with a one-way ANOVA test (followed by LSD Fisher post-hoc test) or Kruskal–Wallis ANOVA test. However, caution is needed when interpreting data of these subgroups because there were only two patients in the neurologic group. Within each group, differences were analysed by a paired Student's *t*-test or Wilcoxon test. Pearson's correlations and multiple regression analyses were performed for the whole group of patients between ΔFVC and (1) anthropometric and spirometric parameters, (2) CMAP values, (3) $\Delta P_{I\,max}$, $\Delta P_{E\,max}$ and (4) recovery duration. Proportions were compared with a Fisher test. Statistics were performed with Statistica 6.1 (Statsoft France, Maisons-Alfort, France). Significance was set at $p<0.05$. Data were expressed as mean ± SD.

Results

Baseline data

Clinical data

Seven patients had bilateral paralysis and 16 unilateral paralyses. For 61% of the patients, the etiology of the diaphragm paralysis was unknown or uncertain (idiopathic group). For the others, the diaphragm paralysis was the consequence of trauma (Nos. 12, 19), sequel of surgery (Nos. 4, 9 and 20), neurologic disease such as diabetic polyneuropathy and Laurence–Moon–Bieds (Nos. 15, 23), paraneoplasy (No. 7) or partial diaphragm resection because of a tumor (No. 8).

Pulmonary function

TLC and FRC were 5.2 ± 1.7 l (76 ± 19% predicted) and 3.1 ± 1.1 l (89 ± 29% predicted), respectively. As expected, patients with unilateral paralysis had significantly better baseline pulmonary function than patients with bilateral paralysis (Table 1). However, baseline FVC was lower than the expected value for unilateral paralysis (75% predicted) in seven patients but yielded normal values in three patients (Figure 1). As previously reported,[11] the changes in FVC from sitting to supine position were greater in patients with bilateral than unilateral paralysis (−48 ± 14 vs. −28 ± 14%,

Table 1 Baseline clinical characteristics of patients with diaphragm paralysis.

Patient	Baseline						
	FVC (%pred)	FEV_1 (%pred)	$P_{I\,max}$ (%pred)	CMAP			
				Amplitude (μV)		Latency (ms)	
				Left	Right	Left	Right
Bilateral							
1	45	40	14	80	150	11	11
2	54	49	63	NR	NR	NR	NR
3	43	43	21	40	70	12	11
4	65	50	77	100	63	12	13
5	58	53	25	40	41	9.9	10
6	60	52	29	NR	NR	NR	NR
7	45	50	29	136	37	12	20
Mean ± SD	53 ± 9	48 ± 5	37 ± 24				
Unilateral							
8	97	84	74	NR	600	NR	8
9	126	104	79	120	480	14.2	7.8
10	47	46	23	NR	90	NR	9.8
11	49	49	9	14	100	9.9	7.7
12	60	46	68	NR	70	NR	9.3
13	98	96	93	620	NR	7.6	NR
14	83	64	55	200	100	7.6	10.7
15	72	67	72	90	40	12.8	26.8
16	71	61	79	400	55	7.9	10.8
17	72	70	72	500	NR	8.1	NR
18	76	63	66	280	NR	10.8	NR
19	48	50	73	290	NR	7.4	NR
20	53	46	36	120	NR	8.1	NR
21	48	45	73	450	NR	8.1	NR
22	87	67	47	120	85	8.5	8.2
23	54	52	57	500	NR	6	NR
Mean ± SD	71 ± 23*	63 ± 18*	61 ± 22*				

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1s; $P_{I\,max}$ = maximal inspiratory mouth pressure; CMAP = diaphragm compound muscle action potential; %pred = percentage of predicted normal value, NR = no electromyographic response to phrenic nerve stimulation.

*$p<0.05$ vs. bilateral.

$p<0.01$). No differences in baseline pulmonary function were observed between the groups with different etiology.

Respiratory muscle function

As expected, $P_{I\,max}$ was lower in patients with bilateral paralysis than in patients with unilateral paralysis (Table 1). Nevertheless, $P_{I\,max}$ was lower than expected in five patients with unilateral paralysis (Figure 1). In two of them, $P_{I\,max}$ yielded values normally obtained with bilateral paralysis. On the other hand, $P_{I\,max}$ reached values higher than expected in three patients with unilateral paralysis although FVC was lower than expected. Maximal expiratory pressure was normal and did not differ between the group with unilateral (95 ± 27% predicted) and bilateral (90 ± 34% predicted) paralysis. No differences in baseline mouth pressures were observed between the groups with different etiology.

Phrenic nerve study

Diaphragm paralysis was confirmed by absence of a CMAP in 12 patients or by an abnormal CMAP in 11 patients (Table 1). Patient No. 15 with diabetic polyneuropathy in whom a CMAP was obtained had a longer baseline phrenic nerve conduction time than patients with idiopathic etiology (10 ± 1.1 ms, $n = 7$) or other etiology namely sequel of surgery and paraneoplasy (14 ± 2 ms, $n = 3$). Baseline CMAP was not influenced by whether diaphragmatic paralysis was uni- or bilateral.

Data obtained at follow-up

Pulmonary function

Pulmonary function of patients was followed-up for a median of 15 months (5–131 months). Patients had 6 ± 4 spirometries during follow-up. FVC improvement greater

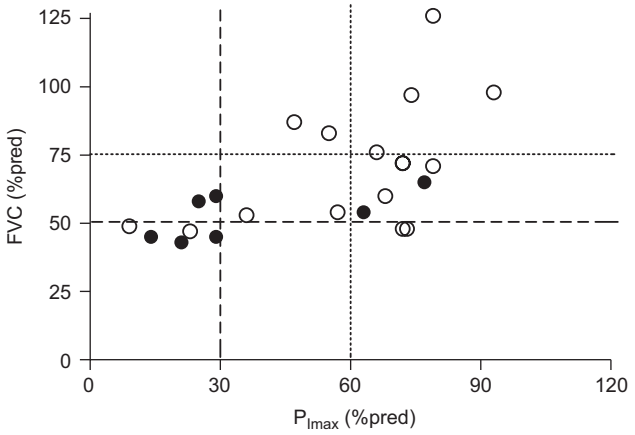

Figure 1 Individual data of forced vital capacity (FVC) and maximal inspiratory pressure ($P_{I\,max}$) at baseline in patients with unilateral (open circles) or bilateral (close circles) diaphragm paralysis. Dotted lines represent the expected value of FVC and $P_{I\,max}$ for patients with unilateral diaphragm paralysis. Dashed lines represent the expected value of FVC and $P_{I\,max}$ for patients with bilateral diaphragm paralysis. FVC and $P_{I\,max}$ are expressed as percentage of the predicted values.

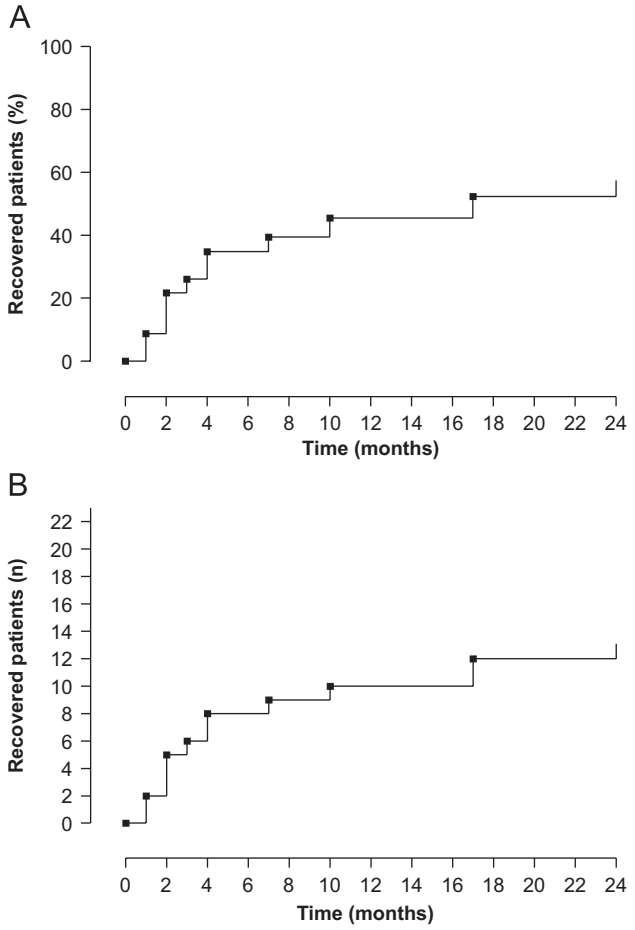

Figure 2 Evolution of functional respiratory recovery for a 24-month follow-up. Data are expressed as a percentage of total amounts of patients (A) and as number of patients (B).

than 400 ml was seen in 35% of the patients after 6 months (eight patients out of 23), in 43% after 1 year (10 out of 23) and in 52% after 2 years (12 out of 23) (Figure 2). Patient anthropometric characteristics did not change significantly over time (except for age). Functional respiratory recovery occurred in 50% and in 71% of the patients with unilateral or bilateral paralysis, respectively ($\chi^2 = 0.9$, $p = 0.3$). Half of the patients with either an idiopathic ($n = \frac{7}{14}$) or another etiology ($n = \frac{4}{7}$) and the two patients with a neurologic disease recovered. FVC improved beyond 400 ml in one of the three patients with unilateral paralysis and normal baseline FVC. Baseline data were similar in the FR and NFR groups (Table 2). By definition, the FR group had a greater improvement in pulmonary function than the NFR group (Table 3).

In 10 patients, FVC decreased either after an initial increase beyond 400 ml (named relapse for the FR group, $n = 5$) or compared with baseline (NFR group, $n = 5$). In the FR group, the etiology of relapse was unknown (three patients), or was due to respiratory muscle training cessation (one patient), or progressing type 2 diabetes mellitus neuropathy (one patient). In the NFR group, FVC decrease coincided with training cessation (three patients), an associated event (two patients). Pulmonary function improvement was not different according to type of paralysis (uni- or bilateral) or etiology.

Respiratory muscle function

Changes in $P_{I\,max}$ tended to be larger in the FR group ($p = 0.1$) while the $P_{E\,max}$ remained unchanged over time. Improvement in $P_{I\,max}$ was related to improvement in FVC ($r = 0.7$, $p < 0.001$).

Respiratory muscle training was started within 1 month after the baseline FVC measurement in 20 patients (0.8 ± 2 months) and after 45 months in one patient. Two patients did not participate to this training. Training lasted 22 ± 24 months. $P_{I\,max}$ ($\Delta P_{I\,max}$, 17 ± 15% predicted, $p < 0.001$) and FVC (ΔFVC, 195 ± 330 ml, 5 ± 8% predicted, $p < 0.01$) were significantly increased at the end of training independently of disease etiology and type of paralysis (uni- or bilateral). Within the FR group, one patient did not train, one recovered before starting training while the 11 other patients recovered 9 ± 9 months after training. In the FR group, $P_{I\,max}$ increased significantly by 20 ± 17% predicted ($p < 0.001$) and FVC by 9 ± 9% predicted (343 ± 363 ml, $p < 0.05$). In the NFR group, the increase in $P_{I\,max}$ (12 ± 13% predicted, $p < 0.05$) did not result in functional respiratory recovery. In patients with unilateral paralysis, recovery did not necessarily occur with training.

Phrenic nerve study

Phrenic nerve conduction was reassessed at follow-up in six patients. In four patients with a CMAP response at baseline (Table 1), three still displayed abnormal CMAP at follow-up but two of them showed FR (Table 2). The last patient had a quasi-normal value at follow-up and recovered (Table 4). For the remaining two patients with a CMAP response at baseline, CMAP amplitude and latency did not improve at follow-up while both patients showed FR of the FVC. The fact that patients had uni- or bilateral diaphragm paralysis did not influence CMAP evolution. These data showed that

Table 2 Baseline characteristics of functional respiratory recovery and non-functional respiratory recovery groups.

	Functional recovery group ($n = 13$)	Non-functional recovery group ($n = 10$)
Unilateral/bilateral paralysis	8/5	8/2
FVC L (%pred)	2.6±1 (62±16)	3.05±1.6 (70±26)
FEV_1 L (%pred)	1.9±0.6 (55±12)	2.2±1.1 (63±21)
$P_{I\,max}$ %pred	50±21	58±30
$P_{E\,max}$ %pred	95±25	92±33
No CMAP value	$n = 8$	$n = 4$
CMAP		
Latency (ms)	14±7 ($n = 5$)	12±2 ($n = 6$)
Amplitude (μV)	73±33 ($n = 5$)	71±41 ($n = 6$)

Same abbreviations as in Table 1. $P_{E\,max}$ = maximal expiratory mouth pressure. Values are expressed as mean±SD.

Table 3 Pulmonary function and maximal mouth pressures between baseline and follow-up measurements for functional respiratory recovery and non-functional recovery groups.

	Functional recovery group ($n = 13$)	Non-functional recovery group ($n = 10$)
Recovery follow-up duration (months)	7±8	25±20*
ΔFVC L	0.6±0.2§	−0.1±0.5†
ΔFVC %pred	135§	−2±11†
ΔFEV_1 L	0.3±0.3§	−0.1±0.5*
ΔFEV_1 %pred	9.5±7.5§	−2.3±12*
$\Delta P_{I\,max}$ %pred	16±16 ($n = 12$)‡	1±21 ($n = 7$)$^{\#}$
$\Delta P_{E\,max}$ %pred	2±14 ($n = 12$)	5±14 ($n = 6$)

Same abbreviations as in Table 2; Δ = difference between baseline and follow-up measurements. Values are expressed as mean±SD. Difference between groups. $^{*}p<0.01$; $^{\dagger}p<0.001$; $^{\#}p = 0.1$. Difference compared with baseline: $^{\ddagger}p<0.01$; $^{\S}p<0.001$.

functional respiratory recovery was not necessarily associated with normalization of the CMAP values.

Sensitivity of the nerve conduction study to detect functional diaphragm recovery in the whole group was low (36%, confidence interval 12–68%). Specificity was 32% (confidence interval 11–64%). None of the baseline characteristics (anthropometric characteristics, baseline pulmonary function, baseline CMAP) were predictive of functional respiratory recovery.

Discussion

The present study describes functional respiratory recovery in patients diagnosed with uni- or bilateral diaphragm paralysis. The study showed that functional consequences of uni- or bilateral diaphragm paralysis are partially reversed in 43% of patients after 1 year, but improvement was not predictable from baseline measurements such as pulmonary function or phrenic nerve conduction parameters. Type of paralysis (uni- or bilateral) and disease etiology did not influence functional respiratory recovery. Inspiratory muscle training is feasible but whether respiratory muscle training was associated with pulmonary function improvement remains uncertain.

In the present study, patients were not actively recruited. Only the patients referred to our center for whom an electromyographic examination was asked by the consulted chest physician were included. In addition, patients with disease known to deteriorate (e.g. spinal ALS) were not included, as recovery is not expected in this population. In the past 11 years, 23 patients were diagnosed with diaphragm paralysis in our hospital, demonstrating the low incidence of this pathology. It may be possible that the incidence of this pathology was underestimated since only the patients referred to our center or those developing the problem in our university hospital were included in the present study. But, on the other hand, these cases may also represent the most complex ones while in the primary or secondary center diagnosis might have been associated with spontaneous recovery not necessitating further investigation. In the present study, most cases were unilateral as previously reported.[5–7] Diaphragm paralysis in our patients was long standing with recovery extended to more patients when follow-up was longer. Average time from diagnosis to FR (6 months for 35% of the patients, 1 year for 43% of the patients and 2 years for 52% of the patients) is similar to that previously described by Wilcox et al.[19] Type of diaphragm paralysis (uni- or bilateral) and its etiology did not significantly influence FR or CMAP value at recovery. Delay of recovery was not linked to severity of baseline phrenic nerve alteration. Moreover, the absence or presence of electromyographic response to phrenic nerve stimulation at baseline was not indicative of CMAP improvement. This study may have been too small or conducted in a too heterogeneous group of patients to exclude the role of electromyography in predicting prognosis. However, in clinical practice, clinicians will always have to deal with small and heterogeneous groups.

Retrospective studies have inherent limitations. As with any long-term retrospective study, not all the patients performed all the tests at each hospital visit (maximal respiratory muscle force, phrenic nerve conduction study) and they were not evaluated at regular time intervals although all visits were supervised by the same treating

Table 4 Clinical characteristics of patients with diaphragm paralysis at recovery follow-up. Same abbreviations as in Tables 1 and 2; time = time elapsed between "recovery" follow-up and baseline data measurement.

Patient	Recovery follow-up							
	ΔFVC (ml)	$\Delta P_{I\,max}$ (%pred)	Time (months)	CMAP				Follow-up total duration (months)
				Amplitude (μV)		Latency (ms)		
				Left	Right	Left	Right	
Bilateral								
1*	490	6	7	–	–	–	–	131
2*	460	12	11	NR	80	NR	13.7	11
3	30	5	7	–	–	–	–	7
4	260	20	11	160	100	10.5	10.3	19
5*	560	0	2	–	–	–	–	23
6*	630	7	30	160	60	10.9	16.2	43
7*	510	28	14	–	–	–	–	105
8*	680	21	4	–	–	–	–	37
9	−240	9	9	130	380	14.6	7.7	9
10	360	–	27	–	–	–	–	39
Unilateral								
11	−360	–	68	–	–	–	–	104
12*	430	4	4	–	–	–	–	15
13	−270	−4	9	600	30	7.3	10	13
14	110	–	15	–	–	–	–	15
15*	520	1	1	–	–	–	–	5
16	−1280	−36	45	–	–	–	–	65
17	80	−11	34	–	–	–	–	34
18*	440	7	10	700	500	11.6	10.2	21
19	230	–	29	–	–	–	–	29
20*	1130	16	2	–	–	–	–	69
21*	440	46	1	–	–	–	–	12
21*	600	42	17	–	–	–	–	20
23*	490		12	–	–	–	–	62

*Recovered patient, – no data available.

physician (MD). However, the aim of this analysis was to characterize potential for recovery after diaphragm paralysis and to investigate whether any measurement performed at baseline would be predictive of favorable outcome. We feel that the present retrospective study serves this aim as all consecutive patients with diaphragm paralysis followed in our center between 1994 and 2005 have been included in the analysis. To our knowledge, the follow-up duration is one of the longest (up to 131 months) and the patient group one of the largest studied to date.[7,12,13,15–19]

In the present study, functional impairment was assessed using spirometry. This technique has been shown to be reproducible in sick and elderly subjects and is easily applied in clinical routine.[20,25,26] Intra-session reproducibility of FVC is generally reported to be within 120–150 ml[20] and intersession reproducibility to be less than 6% of baseline FVC.[25,26] Hence, an increase in FVC beyond 400 ml as used in the present study clearly represents more than the expected error range and should indicate physiological and probably clinically relevant improvement. In our study, impairment of patients with unilateral and bilateral diaphragm paralysis was well within the expected range for baseline FVC,[3,15,27] FEV_1,[27] $P_{I\,max}$ and $P_{E\,max}$.[28] The fact that some patients with unilateral diaphragm paralysis had baseline FVC within normal limits has already been reported previously.[19] Decrease in FVC in supine position was also comparable to that reported by Davis et al.[1]

Besides, FVC appeared to be normalized earlier than CMAP value. Since FVC reflects global inspiratory muscle function and CMAP is representative of the diaphragm only, normalization of FVC earlier than CMAP is conceivable. It remains speculative whether this recovery is enhanced by inspiratory muscle training as no control group was studied. FVC improvement was less than $P_{I\,max}$ improvement and not high enough to result in functional respiratory recovery. Interestingly, it should be noted that 10 patients showed relapse or decreased FVC compared with baseline measurement. For three patients of the NFR group, worsening of FVC occurred while respiratory muscle training was stopped. However, the beneficial effect of respiratory muscle training is difficult to determine in the present study since no control group was studied.

This study alerts clinicians that a potential relapse after an initial improvement may occur in a relatively large portion (26%) of the patients. This has never been reported previously, and surely merits further attention.

Unfortunately, neither baseline pulmonary function, nor baseline respiratory muscle function were predictive of functional respiratory recovery.

Another technique used in the present study to assess functional impairment was the phrenic nerve conduction study. Although today several techniques such as motion and imaging techniques are available to analyze diaphragm function, CMAP measurement in response to phrenic nerve stimulation is a well-established technique to characterize phrenic nerve dysfunction[8] and proved to be a helpful tool in differential diagnosis of diaphragm paralysis.[29] Methodological weaknesses of electrical stimulation technique have been previously described[24,30] such that only the major difficulties will be addressed here. The most significant disadvantage reported with electrical stimulation is discomfort caused by the intensity stimulus. Although this may be painful, it remains, however, relatively well tolerated by the patients. In subconscious and sedated patients, this technique is routinely applied without major difficulties. Locating the phrenic nerve may require some practice but is feasible for an expert performing this test routinely. Actually, location of both phrenic nerves in all subjects tested is not a limiting factor as previously reported by several groups.[8,9,30,31] Attention should also be paid to potential co-stimulation of the plexus brachial during stimulation of the phrenic nerve. This may contaminate the CMAP signal. This co-stimulation is obvious when the arm is moving during the stimulation. In addition, this co-stimulation will result in an initial positive deflection on the CMAP signal. Adjustment of the electrode position is necessary to rule out the plexus brachial signal. CMAP signal may also be affected by the ECG signal. Actually, the morphology of the ECG signal is very similar to that of the CMAP. But ECG artefact occurs randomly while CMAP is time locked to the stimulus, at such they can be distinguished from each other. Another important issue with electrical stimulation is the absence of response. This may be true but this may represent a technical problem to record CMAP (false negative response). In that case, consecutive trials while adjusting location of the electrode (stimulating and pick-up electrodes) as well as stimulus pulse and strength need to be performed to ensure the validity of no response.

In the present study, the above-mentioned points were taken into account to ensure reliability of the measurements. Our data show that phrenic nerve conduction time at baseline was prolonged on the affected side, consistent with phrenic nerve dysfunction. In addition, low $P_{I\,max}$ and normal $P_{E\,max}$ values were consistent with isolated diaphragm paralysis rather than generalized respiratory muscle weakness. However, baseline phrenic nerve conduction studies were not predictive of functional respiratory recovery. Perhaps, functional respiratory recovery may be predicted by techniques other than phrenic nerve stimulation. Lisboa et al.[15] highlighted that in patients with unilateral diaphragm paralysis other respiratory muscles became active during quiet breathing to compensate for the impaired diaphragmatic function.

In conclusion, the present study showed that functional respiratory recovery occurred in 43% of the patients 1 year after diaphragm paralysis diagnosis and in 52% of the patients after 2 years. Type or etiology of the paralysis did not influence functional respiratory recovery. Respiratory muscle training may help to improve pulmonary function independently of paralysis type and disease etiology. Unfortunately, functional respiratory recovery could not be predicted from routine assessment performed in regular clinical work-up. However, the present study may help clinicians to inform patients about prognosis of isolated uni- or bilateral diaphragm paralysis. It shows that FR of diaphragm paralysis may occur late after the onset of paralysis.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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