A retrospective cohort study of idiopathic diaphragmatic palsy: a diagnostic triad, natural history and prognosis

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Tests of respiratory muscle strength are valuable in the diagnostic workup of patients with unexplained dyspnoea. A triad of 1) orthopnoea with 2) normal lung imaging and 3) MEP/MIP and/or MEP/SNIP ratios ⩾2.7 points towards isolated diaphragmatic palsy. https://bit.ly/2SpOXW2

Cite this article as: Nafisa S, Messer B, Downie B, *et al*. A retrospective cohort study of idiopathic diaphragmatic palsy: a diagnostic triad, natural history and prognosis. *ERJ Open Res* 2021; 7: 00953-2020 [DOI: 10.1183/23120541.00953-2020].

Received: 18 Dec 2020
Accepted: 21 June 2021

Abstract

Background Isolated diaphragmatic palsy in the absence of progressive neuromuscular disease is uncommon. It poses diagnostic challenges and limited data are available regarding prognosis. We present retrospective cohort data from two large teaching hospitals in the United Kingdom.

Method 60 patients who were assessed either as inpatients or outpatients were included in this study. Patients with progressive neuromuscular disease were excluded. Clinical presentation, tests of respiratory muscle function (sitting/supine vital capacity, maximal expiratory pressure (MEP), maximal inspiratory pressure (MIP) and sniff nasal inspiratory pressure (SNIP)) and outcomes were recorded.

Results For patients with diaphragmatic palsy, mean±SD seated and supine vital capacity pre-noninvasive ventilation (NIV) were reduced at 1.7±1.2 L and 1.1±0.9 L, respectively, with a mean±SD postural fall in vital capacity of 42±0.16%. The mean MEP/MIP and MEP/SNIP ratios for diaphragmatic palsy were 3 and 3.5, respectively. After a year of treatment with NIV, mean±SD upright and supine vital capacity had increased to 2.1±0.9 L and 1.8±1 L, respectively, and the mean±SD fall in vital capacity from sitting to supine reduced to 29±0.17%. MEP/MIP and MEP/SNIP ratios reduced to 2.6 and 2.9, respectively, from the pre-NIV values. The values of postural fall in vital capacity correlated ($p<0.05$) with MEP/MIP and MEP/SNIP ratio ($r^2=0.86$ and $r^2=0.7$, respectively).

Conclusion Tests of respiratory muscle strength are valuable in the diagnostic workup of patients with unexplained dyspnoea. A triad of 1) orthopnoea, with 2) normal lung imaging and 3) MEP/MIP and/or MEP/SNIP ratio ⩾2.7 points towards isolated diaphragmatic palsy. This needs to be confirmed by prospective studies.

Introduction

The diaphragm is the main inspiratory muscle, and diaphragmatic weakness can lead to respiratory failure. Diaphragmatic weakness or paralysis commonly presents in association with more generalised neuromuscular disorders. However, it can be caused by other pathologies, such as trauma, compression, infection and inflammation [1]. Isolated diaphragmatic palsy is well described [2], but often missed in adults [3], especially in bilateral diaphragmatic palsy (BDP) in which both domes of the diaphragm are elevated.

The evaluation of suspected diaphragmatic palsy typically includes chest radiography and an assessment of pulmonary function, often in the context of unexplained dyspnoea. Dynamic imaging tests used to diagnose diaphragmatic palsy, such as diaphragm fluoroscopy, have low specificity for both unilateral

diaphragm paralysis (UDP) and BDP [4–6]. A drop in vital capacity (VC) of >25% from the upright to the supine position is highly suggestive of diaphragmatic palsy [7, 8]. However, the percentage fall in supine VC cannot be used in subjects who are unable to lie flat, nor in those who cannot easily stand (for example those who are critically ill or wheelchair-bound).

Respiratory muscle tests are used to investigate inspiratory and expiratory muscle strength [9–11]. Maximum inspiratory pressure (MIP) and sniff nasal inspiratory pressure (SNIP) reflect overall inspiratory muscle strength and are usually reduced in patients with diaphragmatic palsy [12], while maximum expiratory pressure (MEP) is an indicator of expiratory muscle strength, which is typically preserved or minimally decreased in patients with isolated diaphragmatic palsy [8, 10]. As a result, the ratio obtained by dividing MEP by MIP gives a ratio >3.0 in BDP [12].

Noninvasive ventilation (NIV) is well established as an effective treatment for diaphragmatic palsy, alleviating orthopnoea and correcting nocturnal hypoventilation. We have conducted a retrospective analysis of cohort data from two large teaching hospitals in the United Kingdom, which aimed to review the causes, presentation, investigation and prognosis of patients with diaphragmatic palsy who required NIV. In addition, the study investigated the suitability of MEP/MIP and MEP/SNIP ratios as diagnostic tests for diaphragmatic palsy in patients who are unable to lie supine.

Methods

A retrospective cohort study was performed on patients with isolated diaphragmatic palsy admitted to hospital or referred as respiratory outpatients for NIV at two large teaching hospitals in the United Kingdom between 2000 and 2020. The diagnosis of isolated diaphragmatic palsy was made on the basis of clinical presentation and findings of elevated hemidiaphragm(s) on chest radiograph. 18 patients also underwent ultrasound examination; mostly two-dimensional echocardiography with M mode performed in a few cases. Progressive neuromuscular disease was excluded after taking a personal and family history, combined with clinical neurological examination and, if indicated, neurological investigation.

Respiratory muscle tests (MEP, MIP and SNIP), together with sitting and supine VC, were recorded at presentation. There are a few different equations for predicted values. We used values from Wilson and co-workers [13–15]. The MEP/MIP and MEP/SNIP ratios were obtained by dividing the value of MEP by the value of MIP and the value of MEP by the value of SNIP, respectively.

All the subjects in this study were deemed to require respiratory support and were commenced on NIV. The indications for NIV were diurnal hypercapnic respiratory failure, symptomatic nocturnal hypoventilation or difficulty in weaning. After 1 year, measurements of respiratory muscle strength and VC were repeated.

Statistical analyses were undertaken using GraphPad Prism version 8.4.3, taking 0.05 as the level of statistical significance. The spirometric and maximal static pressure measurements were normally distributed. Spearman rank correlation was used to test the correlation between postural fall in VC with MEP/MIP and MEP/SNIP ratio. A paired t-test was used to observe the relationship between pre-NIV and post-NIV measurements. Receiver operating characteristic (ROC) curves were constructed to determine the cut-off for both MEP/MIP and MEP/SNIP ratios in comparison with seated to supine fall in VC to detect diaphragmatic palsy.

Results

60 patients with diaphragmatic palsy were included in the study. Their mean±SD age was 58±12.9 years (range 25–72 years). 38 were male. 29 had UDP and 31 had BDP. The aetiology of diaphragmatic palsy is listed in table 1. In the subjects where there was a clear cause for diaphragmatic palsy, the most common procedure was heart–lung transplantation, reflecting the specialist interest on one of our centres.

The mode of presentation of these patients with diaphragmatic palsy was diverse. 22 (36%) patients presented post-operatively or after intensive care unit (ICU) admission; 13 (21%) patients presented acutely with hypercapnic respiratory failure; and 19 (31%) patients were referred to a respiratory outpatient clinic.

All 60 patients had elevation of one or both hemidiaphragms on chest radiography and 18 patients had ultrasonographic evidence of diaphragmatic palsy. Dyspnoea on exertion, orthopnoea and difficulty in weaning ventilation were the main clinical presentations (table 2). 10 patients had paradoxical diaphragmatic movement on clinical examination. 19 patients had more than one symptom.

TABLE 1 Aetiology of diaphragm paralysis

	Patients n
Idiopathic	31
Post-heart–lung transplant	18
Post-coronary artery bypass grafting	2
Post-radiofrequency cardiac ablation	2
Post-spinal surgery	1
Post-thyroidectomy	1
Post-mastectomy	1
Post-radiotherapy	1
Post-intensive care unit admission	1

Spirometry and respiratory muscle tests in 40 subjects at presentation are shown in table 3. (20 patients were too unwell to perform seated and supine manoeuvres at the time of their diagnosis of diaphragmatic palsy.) As expected, there was a significant postural fall in VC, well-preserved MEP, but low MIP and SNIP. The mean MEP/MIP and MEP/SNIP ratios were ⩾3.0. Postural fall in VC correlated with MEP/MIP (r^2=0.76) and MEP/SNIP (r^2=0.68) (figure 1a and b). ROC curves (figure 1c and d) comparing postural fall in VC with MEP/MIP and MEP/SNIP yielded area under the curve 0.86 (95% CI 0.77–0.9) and 0.82 (95% CI 0.74–0.92), respectively, with an optimal cut-off of 2.7 for both ratios. All patients with MEP/MIP and/or MEP/SNIP ratios ⩾2.7 had a drop in supine VC of ⩾25%.

1 year after their initial assessment, eight subjects had discontinued NIV due to improvement in diaphragmatic function. 14 subjects had died, in all cases from causes unrelated to their diaphragmatic palsy. Six of the deaths were in heart–lung transplant patients. None of the patients developed a malignancy, nor a more generalised neurological disorder during the year of follow-up. The respiratory muscle test results for the 38 patients still using NIV are included in table 3, and they continue to have elevation of one or both hemidiaphragms.

Discussion

Depending on the disease severity, patients with diaphragmatic palsy present with a range of symptoms, including dyspnoea on exertion, reduced exercise tolerance, orthopnoea and dyspnoea or orthopnoea that may be attributed to comorbid conditions such as obesity or cardiopulmonary diseases [7, 11, 16, 17]. When their dyspnoea becomes physically limiting, they usually present to respiratory physicians [18]. Diaphragmatic palsy is not uncommon but there can often be a delay in diagnosis because lung fields are clear on radiological imaging, provided there is no other coexisting pathology. Fluoroscopy can be misleading, as can ultrasound imaging, particularly in cases of BDP. There is often a delay in requesting respiratory muscle strength tests and patients are not always able to perform supine VC manoeuvres. Transdiaphragmatic pressure measurements or electrical/magnetic stimulation of phrenic nerve requires considerable expertise and sophisticated equipment, which are not widely available [9].

The percentage drop in VC from sitting to supine is regarded as a screening test for diaphragmatic palsy with normal values ranging from 3% to 9%, whereas a drop in VC of 10–20% in the supine position is suggestive of UDP [7, 16]. A postural drop in VC from sitting/upright to supine position is generally used

TABLE 2 Symptoms and clinical signs in 60 patients with diaphragm paralysis at presentation

	Patients n
Dyspnoea on exertion	28
Orthopnoea	32
Paradoxical abdominal motion	10
Difficulty in weaning from ventilation	10
Morning headaches	9
Daytime somnolence	9
Immersion dyspnoea	3
Post-operative nocturnal desaturation	3
Sleep disturbance	3

TABLE 3 Lung function at presentation and after 1 year of noninvasive ventilation (NIV)

	At presentation	After 1 year of NIV	p-value
Seated VC (L)	1.7±1.2	2.1±0.9	<0.001
Seated VC (% pred)	49±0.17	60±0.2	<0.001
Supine VC (L)	1.1±0.9	1.8±1	<0.001
Fall in VC seated to supine (% seated)	42±0.16	29±0.17	<0.001
MEP (cmH_20)	103±8	132±7	0.14
MEP (% pred)	84±4	96±6	0.19
MIP (cmH_20)	34±10	50±8	0.27
MIP (% pred)	32±5	63±5	0.31
SNIP (cmH_20)	29±5	47.5±7	<0.001
SNIP (% pred)	28±3	42±2	<0.001
MEP/MIP ratio	3±1.2	2.6±1.4	<0.001
MEP/SNIP ratio	3.5±1.9	2.9±1.7	<0.001

Data are presented as mean±SD, unless otherwise stated. VC: vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; SNIP: sniff nasal inspiratory pressure.

to characterise the severity of diaphragmatic palsy [18]. The gravitational shifts in abdominal contents that displace the diaphragm cephalad, a shift in blood volume into the thorax and the mechanical disadvantage of intercostal muscles in the supine position cause this reduction in VC [19]. A fall in VC from sitting to supine of ⩾25% indicates diaphragm weakness, with the degree of decline in VC percentage from sitting to supine correlating with the severity of dyspnoea [8, 17].

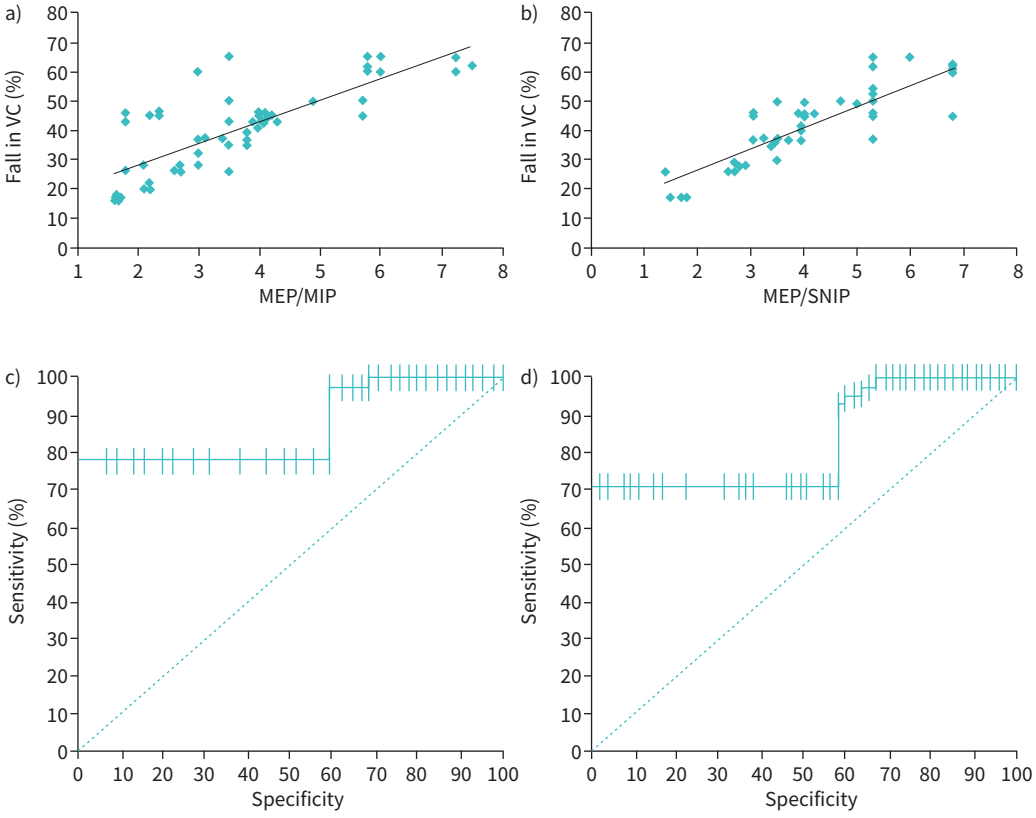

FIGURE 1 Scatterplots of a) maximal expiratory pressure (MEP)/maximal inspiratory pressure (MIP) and b) MEP/sniff nasal inspiratory pressure (SNIP) against fall in seated to supine vital capacity (VC) at presentation in subjects with diaphragm paralysis (a) r^2=0.76, b) r^2=0.68; p<0.05). Receiver operating characteristic curves comparing the percentage postural fall in VC with c) MEP/MIP and d) MEP/SNIP.

However, supine measures of VC are hard to perform in those with severe diaphragmatic palsy who are unable to lie flat or are wheelchair-bound. Critically ill patients are also unable to perform supine and seated manoeuvres. Tests of respiratory muscle function that include MEP, MIP and SNIP manoeuvres can easily be performed with patients in the seated position. Our findings support the proposal of Koo *et al.* [12] that MEP/MIP ⩾3 has the potential to be used as a screening tool for diaphragmatic palsy. Our cut-off of 2.7 would provide higher sensitivity than a cut-off of 3.0, and can be extended to MEP/SNIP ratio, but this needs to be confirmed by prospective studies. Screening for diaphragmatic palsy at an earlier stage could lead to more timely referrals to a specialist centre for further management of the condition. It is important to note that MIP and SNIP are not specific to the diaphragm, but include inspiratory force generated by intercostal and accessory muscles. Some of the changes seen in MEP/MIP and MEP/SNIP ratio could be explained by training up of intercostal and accessory muscles, rather than recovery in the strength of the diaphragm itself [20].

Our patients all had diaphragmatic palsy of significant severity to require NIV, even although the diaphragmatic palsy was apparently only unilateral. With the use of NIV, the majority of patients with diaphragmatic palsy experience improvement in their clinical symptoms. Use of NIV allows time for recovery of diaphragmatic strength to occur. Spontaneous recovery is well documented in subjects with diaphragmatic palsy [21], usually occurring within 1 year of diagnosis [22]. The majority of our subjects continued to require NIV 1 year after diagnosis, despite showing some improvement in diaphragmatic function (based on a smaller change in VC from sitting to supine and a reduction in MEP/MIP and MEP/SNIP ratios). Diaphragmatic palsy is well recognised after cardiothoracic surgery, due to injury to the phrenic nerve. Asymptomatic subjects with post-surgical diaphragmatic palsy do not require treatment, but those with symptoms will need NIV. In our cohort, an improvement in clinical symptoms was noted in all patients with post-surgical diaphragmatic palsy following treatment with NIV, but they did not recover fully.

The role of surgical plication of the diaphragm in diaphragmatic palsy remains unclear, but it should probably be delayed until at least a year after diagnosis, in order to allow time for the possibility of spontaneous recovery [23, 24]. Close observation during the first year after diagnosis of diaphragmatic palsy is important in order to assess whether there has been spontaneous recovery, in which case NIV may no longer be required. The patient's circumstances may have changed such that NIV is no longer appropriate, as was the case in several of our subjects. Regular measurement of MEP/SNIP or MEP/MIP ratios would reveal whether there is deterioration of diaphragm strength, or the development of expiratory muscle weakness, prompting careful neurological re-evaluation. None of our patients developed a generalised muscle disorder over the study period, although this may manifest itself until several years after the diagnosis of diaphragmatic palsy. For unexplained orthopnoea with normal chest imaging, a selective reduction in inspiratory pressure (MEP/MIP and/or MEP/SNIP ratio ⩾2.7) will be useful for diagnosing isolated BDP. Conversely, reduction in expiratory and inspiratory pressures to similar values would suggest a generalised neurological condition such as motor neurone disease or a myopathy. In patients with sequential diaphragmatic palsy, one hemidiaphragm may be more significantly affected than the other, leading to a radiographic appearance of unilateral palsy. If they demonstrate a >25% drop in VC with MEP/MIP (or MEP/SNIP) ratio ⩾2.7, they are likely to have BDP and are more likely to benefit from nocturnal NIV [20]. This highlights the need for checking supine VC and respiratory muscle strength if patients' symptoms are disproportionate to imaging.

Limitations

Our study has a few limitations. We have included patients with diaphragmatic palsy admitted to hospital and referred to an outpatient clinic, while we excluded patients with progressive neuromuscular disorder. The MEP/MIP and MEP/SNIP ratios may not be applicable to this population as expiratory muscles are affected in neuromuscular disease.

Conclusion

Isolated diaphragmatic palsy can be difficult to diagnose and is often missed in adults with unexplained dyspnoea. Early diagnosis may lead to early referral to a specialist centre for further management. A triad of 1) orthopnoea with 2) normal lung imaging and 3) MEP/MIP or MEP/SNIP ratios ⩾2.7 is very highly suggestive of isolated BDP (as defined by supine drop in VC of 25%) in patients without progressive neuromuscular disease and in those without obstructive spirometry. This triad (particularly after prospective confirmation of MEP/MIP and MEP/SNIP cut-off) could be used where patients are unable to perform supine VC manoeuvre (critically ill patients or those in ICU). NIV leads to a significant symptomatic improvement and is associated with good long-term outcome and survival. Our data show that this population treated timely with NIV demonstrates good symptomatic relief and has a good prognosis.

Provenance: Submitted article, peer reviewed.

Ethical statement: This is a retrospective study involving outpatients and inpatients in two hospitals. Ethical approval was not required.

Conflict of interest: None declared.

References

1 Polkey M, Lyall R, Moxham J, *et al.* Respiratory aspects of neurological disease. *J Neurol Neurosurg Psychiatry* 1999; 66: 5–15.
2 Dubé B-P, Dres M. Diaphragm dysfunction: diagnostic approaches and management strategies. *J Clin Med* 2016; 5: 113.
3 Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003; 168: 10–48.
4 Polkey M, Green M, Moxham J. Measurement of respiratory muscle strength. *Thorax* 1995; 50: 1131–1135.
5 Steier J, Kaul S, Seymour J, *et al.* The value of multiple tests of respiratory muscle strength. *Thorax* 2007; 62: 975–980.
6 Laroche C, Mier A, Moxham J, *et al.* Diaphragm strength in patients with recent hemidiaphragm paralysis. *Thorax* 1988; 43: 170–174.
7 Laroche C, Carroll N, Moxham J, *et al.* Clinical significance of severe isolated diaphragm weakness. *Am Rev Respir Dis* 1988; 138: 862–866.
8 Black L, Hyatt R. Maximal static respiratory pressures in generalized neuromuscular disease. *Am Rev Respir Dis* 1971; 103: 641–650.
9 Mills G, Kyroussis D, Hamnegard C, *et al.* Cervical magnetic stimulation of the phrenic nerves in bilateral diaphragm paralysis. *Am J Respir Crit Care Med* 1997; 155: 1565–1569.
10 Hart N, Nickol A, Cramer D, *et al.* Effect of severe isolated unilateral and bilateral diaphragm weakness on exercise performance. *Am J Respir Crit Care Med* 2002; 165: 1265–1270.
11 Lisboa C, Paré P, Pertuzé J, *et al.* Inspiratory muscle function in unilateral diaphragmatic paralysis. *Am Rev Respir Dis* 1986; 134: 488–492.
12 Koo P, Oyieng'o D, Gartman E, *et al.* The maximal expiratory-to-inspiratory pressure ratio and supine vital capacity as screening tests for diaphragm dysfunction. *Lung* 2017; 195: 29–35.
13 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
14 Wilson SH, Cooke NT, Edwards RHT, *et al.* Predicted normal values for maximal respiratory pressures in Caucasian adults and children. *Thorax* 1984; 39: 535–538.
15 Héritier F, Rahm F, Pasche P, *et al.* Sniff nasal inspiratory pressure. A noninvasive assessment of inspiratory muscle strength. *Am J Respir Crit Care Med* 1994; 150: 1678–1683.
16 Gibson GJ. Diaphragmatic paresis: pathophysiology, clinical features, and investigation. *Thorax* 1989; 44: 960–970.
17 Allen S, Hunt B, Green M. Fall in vital capacity with posture. *Br J Dis Chest* 1985; 79: 267–271.
18 Fromageot C, Lofaso F, Annane D, *et al.* Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. *Arch Phys Med Rehabil* 2001; 82: 123–128.
19 Verin E, Marie J-P, Tardif C, *et al.* Spontaneous recovery of diaphragmatic strength in unilateral diaphragmatic paralysis. *Respir Med* 2006; 100: 1944–1951.
20 LoMauro A, Privitera E, Aliverti A, *et al.* Sniff test: does what we measure at the nose reflect what happens in the chest wall? *Clin Respir J* 2020; 14: 589–591.
21 Gayan-Ramirez G, Gosselina N, Troosters T, *et al.* Functional recovery of diaphragm paralysis: a long-term follow-up study. *Respir Med* 2008; 102: 690–698.
22 Ciccolella DE, Daly BD, Celli BR. Improved diaphragmatic function after surgical plication for unilateral diaphragmatic paralysis. *Am Rev Respir Dis* 1992; 146: 797–799.
23 Simansky DA, Paley M, Refaely Y, *et al.* Diaphragm plication following phrenic nerve injury: a comparison of paediatric and adult patients. *Thorax* 2002; 57: 613–616.
24 Elamin EM, Wilson CS, Sriaroon C, *et al.* Effects of early introduction of non-invasive positive pressure ventilation based on forced vital capacity rate of change: variation across amyotrophic lateral sclerosis clinical phenotypes. *Int J Clin Pract* 2019; 73: e13257.