ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original article

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

Syeda Nafisa, Ben Messer, Beatrice Downie, Patience Ehilawa, William Kinnear, Sherif Algendy, Milind Sovani

Please 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; in press (https://doi.org/10.1183/23120541.00953-2020).

A Retrospective Cohort Study of Idiopathic Diaphragmatic Palsy: A Diagnostic Triad, Natural History and Prognosis.

Authors

Syeda Nafisa[1,5], Ben Messer[2], Beatrice Downie[3], Patience Ehilawa [1,5], William Kinnear[4] , Sherif Algendy[5], Milind Sovani.[1]

Affiliations:

1. Respiratory Medicine, Nottingham University Hospitals,

   Nottingham, United Kingdom

2. North East Assisted Ventilation Service, Newcastle Upon Tyne Hospital NHS Foundation Trust, United Kingdom

3. Department of Respiratory Medicine, Newcastle Upon Tyne Hospital NHS Foundation Trust, United Kingdom

4. Department of Sport Science, Nottingham Trent University, Nottingham, United Kingdom.

5. Department of Respiratory Medicine, Sherwood Forest Hospital NHS Foundation Trust, Mansfield, United Kingdom

Correspondence:

Syeda Nafisa, Department of Respiratory Medicine, City Hospital, Nottingham, United Kingdom NG5 1PB

email s.nafisa@nhs.net

Take Home Message

Tests of respiratory muscle strength are valuable in the diagnostic workup of patients with unexplained dyspnoea. A triad of a) orthopnoea with b) normal lung imaging and c) MEP/MIP and/or MEP/SNIP ratios ≥ 2.7 points towards isolated DP.

Keywords: diaphragm, isolated diaphragmatic palsy, respiratory muscle tests, pulmonary function tests

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 (DP) is well-described [2], but often missed in adults [3], especially in bilateral diaphragmatic palsy (BDP) where both domes of the diaphragm are elevated.

The evaluation of suspected DP typically includes chest x-rays and an assessment of pulmonary function, often in the context of unexplained dyspnoea. Dynamic imaging tests used to diagnose DP, 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 DP [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 DP [12], while Maximum Expiratory Pressure (MEP) is an indicator of expiratory muscle strength which is typically preserved or minimally decreased in patients with isolated DP [8, 10]. As a result, the ratio obtained by dividing MEP by MIP gives a ratio >3.0 in BDP (12).

Non-invasive ventilation (NIV) is well-established as an effective treatment for DP, 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 DP who required NIV. The study also investigated the suitability of MEP/MIP and MEP/SNIP ratios as diagnostic tests for DP in patients who are unable to lie supine.

Methods

A retrospective cohort study was performed on patients with isolated DP 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 DP was made on the basis of clinical presentation and findings of elevated hemidiaphragm(s) on chest radiograph. Eighteen patients also underwent ultrasound examination- mostly 2D ECHO 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 et al. (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 non-invasive ventilation (NIV). The indications for NIV were diurnal hypercapnic respiratory failure, symptomatic nocturnal hypoventilation or difficulty in weaning. After one 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 DP.

Results

A total of 60 patients with DP were included in the study. Their mean ± SD age was 58±12.9 years (range 25-72). Thirty-eight were male. Twenty-nine had unilateral diaphragm paralysis (UDP) and 31 had BDP. The aetiology of DP is listed in Table 1. In the subjects where there was a clear cause for DP, 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 DP was diverse. Twenty-two (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 x-ray and 18 patients had USS evidence of DP. Dyspnoea on exertion, orthopnoea and difficulty in weaning ventilation were the main clinical presentations (Table 2). Ten patients had paradoxical diaphragmatic movement on clinical examination. Nineteen patients had more than one symptom.

Spirometry and respiratory muscle tests in 40 subjects at presentation are shown in Table 3. (Twenty patients were too unwell to perform seated and supine manoeuvres at the time of their diagnosis of DP.) As expected, there was a significant postural fall in VC, well preserved MEP but with 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) (Figures a and b). ROC curves (Figures c 1 and c 2) comparing postural fall in VC with MEP/MIP and MEP/SNIP yielded area under curves (AUC) of 0.86 (95% confidence interval 0.77–0.9) and 0.82 (95% confidence interval 0.74–0.92) respectively, with an optimal cut-off of 2.7 for both ratios (Figure d). All patients with MEP/MIP and/or MEP/SNIP ratios ≥ 2.7 had a drop in supine VC of ≥ 25%.

One year after their initial assessment, 8 subjects had discontinued NIV due to improvement in diaphragmatic function. Fourteen subjects had died, in all cases from causes unrelated to their DP. 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 DP present with a range of symptoms, including dyspnoea on exertion, reduced exercise tolerance, orthopnoea and dyspnoea or orthopnoea that may be attributed to co-morbid conditions such as obesity or cardiopulmonary diseases [7,11,16,17]. When their dyspnoea becomes physically limiting, they usually present to respiratory physicians [18]. DP 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 co-existing 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 DP with normal values ranging from 3-9% whereas a drop in vital capacity (VC) of 10 to 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 to characterize the severity of DP. [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 $\geq$ 25% or greater indicates diaphragm weakness, with the degree of decline in VC from sitting to supine percentage correlating with the severity of dyspnoea [8, 17].

Supine measures of VC are however hard to perform in those with severe DP who are unable to lie flat or are wheelchair-bound subjects. 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 that MEP/MIP $\geq$3 has the potential to be used as a screening tool for DP [12]. Our cut-off of 2.7 would provide higher sensitivity than a cut-off of 3 and can be extended to MEP/SNIP ratio but this needs to be confirmed by prospective studies. Screening for DP 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 DP of significant severity to require NIV, even although the DP was apparently only unilateral. With the use of NIV, the majority of patients with DP 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 DP [21], usually occurring within one year of diagnosis [22]. The majority of our subjects continued to require NIV one 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.) DP is well recognised after cardiothoracic surgery, due to injury to the phrenic nerve. Asymptomatic subjects with post-surgical DP 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 DP following treatment with NIV, but they did not fully recover.

The role of surgical plication of the diaphragm in DP 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 DP 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 if 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 DP. For unexplained orthopnoea with normal chest imaging, a selective reduction in inspiratory pressure (MEP/MIP and/or MEP/SNIP ratio $\geq$2.7) will be useful for diagnosing isolated BDP. On the other hand, 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 can be seen. If they demonstrate a >25% drop in VC with MEP/MIP (or MEP/SNIP) ratio $\geq$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 DP 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 DP 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 a) orthopnoea with b) normal lung imaging and c) MEP/MIP $\pm$ MEP/SNIP ratios $\geq$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 or patients in intensive care unit). 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.

Acknowledgements: None.
There was no financial support for this study.

Ethical statement:

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

Conflicts of Interest:
The authors declare no conflict of interest.

References

1. Polkey M, Lyall R, Moxham J, Leigh P. Respiratory aspects of neurological disease. J Neurol Neurosurg Psych 1999;66:5–15.
2 .Dubé B-P, Dres M. Diaphragm Dysfunction: Diagnostic Approaches and Management Strategies. J Clin Med. 2016;5:113. doi:10.3390/jcm5120113
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, Jolley C, Rafferty G, Man W, Luo YM, Roughton M, Polkey M, Moxham J. The value of multiple tests of respiratory muscle strength. Thorax 2007; 62:975–980.
6. Laroche C, Mier A, Moxham J, Green M. Diaphragm strength in patients with recent hemidiaphragm paralysis. Thorax 1988; 43:170–174.
7. Laroche C, Carroll N, Moxham J, Green M. Clinical significance of severe isolated diaphragm weakness. Am Rev Respir Dis 1988;138:862-6. doi:10.1164/ajrccm/138.4.862.
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, Wragg S, Polkey MI, Moxham J, Green M. 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, Ward S, Lofaso F, Pride N, Moxham J, Polkey M. 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, Pare P, Pertuze J, Contreras G, Moreno R, Guillemi S, Cruz E. Inspiratory muscle function in unilateral diaphragmatic paralysis. Am Rev Respir Dis 1986; 134:488–492.
12. Koo P, Oyieng'o D, Gartman E, Sethi J, Eaton C, McCool D. 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, Spiro SG. Predicted normal values for maximal respiratory pressures in Caucasian adults and children. Thorax 1984; 39: 535-8
15: Heritier F, Rahm F, Pasche P, Fitting J-W. Sniff nasal pressure: a non-invasive 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, Falaize L, Lejaille M, Clair B, Gajdos P, Raphael J. Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. Arch Phys Med Rehabil 2001;82:123-128.
19. Verina E, Marieb J-P, Tardifa C, Denisa Ph. Spontaneous recovery of diaphragmatic strength in unilateral diaphragmatic paralysis. Respir Med 2006;100:1944–1951.
20. Sniff test: Does what we measure at the nose reflect what happens in the chest wall? LoMauro A , Privitera E, Aliverti A, et . Clin Respir J 2020;14(6):589-591
21. Gayan-Ramirez G, Gosselina N, Troosters T, Bruyninckx F, Gosselink R, Decramer M.

Functional recovery of diaphragm paralysis: A long-term follow-up study. Resp 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 –9.
23. Simansky DA, Paley M, Refaely Y, Yellin A. 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.

Table-1 Aetiology of diaphragm paralysis.

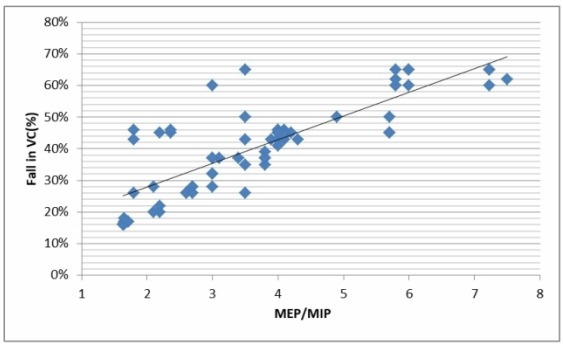
Aetiology	**Number of subjects**
Idiopathic	31
Post heart-lung transplant	18
Post coronary artery bypass grafting	2
Post radio-frequency cardia ablation	2
Post spinal surgery	1
Post thyroidectomy	1
Post mastectomy	1
Post radiotherapy	1
Post intensive care unit admission	1

Table -2 Symptoms and clinical signs in 60 patients with diaphragm paralysis at presentation.

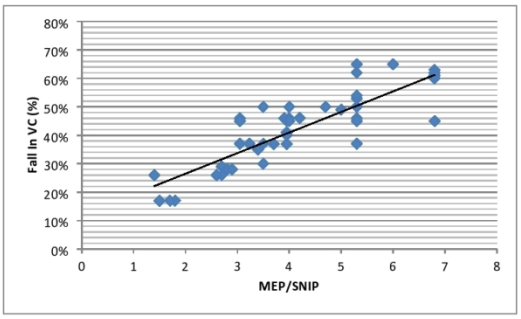
Dyspnoea on exertion	28
Orthopnoea	32
Paradoxical abdominal motion	10
Difficulty in weaning from ventilation	10
Morning headaches	9
Daytime somnolence	9
Immersion dyspnoea	3
Post-operative nocturnal desaturation	3
Sleep disturbance	3

Table -3 Lung Function at presentation and after one year of NIV

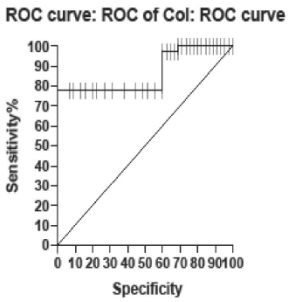
	At presentation	**After one year of NIV**	**P Value**
Seated VC (L)	1.7±1.2	2.1±0.9	<0.001
Seated VC (% pred)	49± 0.17	60± 0.2	<0.001
Supine VC (L)	1.1±0.9	1.8±1	<0.001
Fall in VC seated to supine (% seated)	42±0.16	29 ±0.17	<0.001
MEP (cmH_20)	103±8	132±7	0.14
MEP (% pred)	84±4	96±6	0.19
MIP (cmH_20)	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



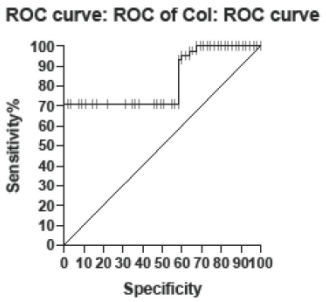
Scatterplot of MEP/MIP against fall in seated to supine VC at presentation in subjects with diaphragm paralysis ($p < 0.05$, $r2 = 0.76$)



Scatterplot of MEP/SNIP against fall in seated to supine VC at presentation in subjects with diaphragm paralysis ($p < 0.05$, $r2 = 0.68$).



Receiver operator characteristic (ROC) curves comparing the percent of postural fall in VC with MEP/ MIP



Receiver operator characteristic (ROC) curves comparing the percent of postural fall in VC with MEP/SNIP .