A case of unexplained dyspnoea: when lung function testing matters!

Lung function corner

“Lung function corner” articles in Breathe present the results of a lung function test and the authors then debate the interpretation, including potential controversies and background from the literature. As section editors of this newly created section of Breathe, we felt it was important to write the first article, which highlights the usefulness of lung function testing in guiding clinical diagnosis especially in difficult cases such as the one we discuss here.

Case history

A 36-year-old physically active man is referred for dyspnoea on exertion such as climbing stairs (three floors), playing soccer, during diving and when speaking for a long time.

He revealed that his symptoms appeared a few days after a cervical manipulation by a physiotherapist due to cervical pain on the left side of his neck. He is a current smoker (5 pack-years). He suffered from Parsonage–Turner syndrome (a brachial plexus neuropathy of uncertain cause characterised by rapid onset of severe pain in the shoulder and arm, that usually resolves in most of the affected individuals) accompanied by right arm deficit in 1996 with no long-term consequences or sequelae. His current body mass index is 26 kg·m$^{-2}$. His Medical Research Council score for dyspnoea is 1–2. He admitted breathlessness while lying in the supine position (orthopnoea) and bending down or over to pick something up, e.g. to tie shoelaces or to garden (antepnoea) but denied breathlessness while lying on the left or right side (lateropnoea). On a recent resting echocardiography, left ventricular ejection fraction was normal. Physical examination during spontaneous resting breathing was strictly normal: chest movement was equally bilateral, there was no abdominal paradox, or inspiratory neck muscle anomalies, or alterations on pulmonary and cardiac auscultation.

Questions

What is the primary cause of his unexplained dyspnoea? Would pulmonary function testing (PFT) including respiratory muscle evaluation be an appropriate means to answer these questions?
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**Answers**

A PFT including respiratory muscle evaluation at this stage would be an appropriate means to identify the cause of dyspnoea. Table 1 presents the results from spirometry and lung volumes in an upright sitting and supine position.

PFT in an upright sitting position clearly showed a restrictive ventilatory defect as characterised by a reduction in TLC below the fifth percentile of the predicted value (LLN), and a normal FEV1/VC [1]. To elucidate the origin of this restrictive ventilatory defect (chest wall or neuromuscular disorders), diffusing capacity of the lung for carbon monoxide (DLCO), arterial blood gas analysis and a respiratory muscle evaluation were performed. Arterial blood gas analysis was normal. DLCO was slightly reduced in absolute value but the transfer coefficient of the lung for carbon monoxide (Kco) was slightly increased, suggesting respiratory muscle or chest wall disease, rather than microvascular or lung parenchymal involvement, therefore making the functional orientation switch more towards neuromuscular disorders. Respiratory muscle evaluation revealed a weakness of the inspiratory muscles (table 2), with a MIP, MEP and SNIP all reduced to 55%, 71% and 50% predicted, respectively [2, 3].

In the presence of potential respiratory muscle weakness, a simple functional test available in PFT laboratories to orient towards diaphragmatic dysfunction is the evaluation of VC in the supine position (table 1). A difference of 35% was found between the VC measured in an upright sitting versus supine position. This finding made us suspect a diaphragmatic dysfunction due to neuralgic amyotrophy (given the history of acute shoulder or neck pain followed by dyspnoea), which was confirmed by the invasive standard procedure involving electrical and magnetic phrenic nerve stimulation with transdiaphragmatic pressure. Of note, on a chest radiograph requested after the lung function testing, he was found to have an elevated right hemidiaphragm. The computed tomography (CT) scan showed no lesions of the right phrenic nerve. The patient was transferred to the pulmonology department for a complete workup. Follow-up muscle evaluations between 1 and 3 years after initial referral showed complete recovery of diaphragmatic function in our patient. Diaphragmatic strength returned very slowly.

**State of the art and controversial issues**

Patients with unilateral diaphragmatic paralysis are usually asymptomatic but may present with exertional dyspnoea and, occasionally, with orthopnoea. Patients with bilateral diaphragmatic

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**Table 1** *Resting PFT in an upright sitting and supine position*

|                  | Measured | LLN   | ULN   | Reference (mean value) | % of reference | Measured | % of reference |
|------------------|----------|-------|-------|------------------------|----------------|----------|----------------|
| VC L             | 4.13     | 4.33  | 6.17  | 5.25                   | 79%            | 2.70     | 51%           |
| TLC L            | 5.79     | 6.07  | 8.37  | 7.22                   | 80%            | 4.17     | 58%           |
| FRC L            | 2.39     | 2.43  | 4.41  | 3.42                   | 70%            | 1.65     | 48%           |
| IC L             | 3.40     | 3.47  | 4.41  | 3.42                   | 98%            | 2.52     | 73%           |
| RV L             | 1.65     | 1.24  | 2.58  | 1.91                   | 87%            | 1.47     | 77%           |
| ERV L            | 0.73     | 1.73  |       |                        | 42%            | 0.18     | 10%           |
| RV/TLC %         | 29       | 19    | 37    | 28                     | 102%           | 35       | 126%          |
| FEV1 L           | 3.07     | 3.32  | 5.00  | 4.16                   | 74%            |          |               |
| FVC L            | 4.04     | 4.03  | 6.03  | 5.03                   | 80%            |          |               |
| FEV1/VC %        | 74       | 69    | 92    | 81                     | 94%            |          |               |
| PEF L·s⁻¹        | 8.11     | 7.59  | 11.57 | 9.58                   | 85%            |          |               |
| FEF25 % L·s⁻¹    | 6.93     | 5.44  | 11.06 | 8.25                   | 84%            |          |               |
| FEF50 % L·s⁻¹    | 3.52     | 3.14  | 7.48  | 5.31                   | 66%            |          |               |
| FEF75 % L·s⁻¹    | 0.91     | 1.11  | 3.67  | 2.39                   | 38%            |          |               |

LLN: lower limit of normality; ULN: upper limit of normality; VC: vital capacity; TLC: total lung capacity; FRC: functional residual capacity; IC: inspiratory capacity; RV: residual volume; ERV: expiratory reserve volume; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; FEFx%: forced expiratory flow measured after x% of the FVC has been exhaled. #: spirometric evidence of an obstructive ventilatory defect as defined by a reduced FEV1/VC ratio less than the fifth percentile of the predicted value [1].
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paralysis or severe diaphragmatic weakness are usually symptomatic and may have considerable dyspnoea on exertion, when lying in the supine position, when immersed in water above their waist, or even at rest. Once suspected, diaphragmatic dysfunction can be confirmed by several tests. Decisions about workup are generally made on the basis of the invasiveness and availability of testing. Definitive diagnosis of diaphragm dysfunction can be obtained by phrenic nerve stimulation combined with diaphragmatic electromyography and/or twitch transdiaphragmatic pressure (twitch \( P_{di} \)) measurement.

Simple and noninvasive PFTs, especially measurements of upright and supine VC which depend on activation of both inspiratory and expiratory muscles [4], are readily available, and may support or refute the suspicion of respiratory muscle dysfunction, especially of the diaphragm (figures 1 and 2) [4–6]. However, the major limitation of upright VC is that MIP decreases earlier than upright VC, this occurs especially in neuromuscular diseases, thus making the suspicion difficult and postponing the correct diagnosis if relying exclusively on upright VC. Unilateral diaphragm weakness is usually associated with a mild decrease in VC, to \( \sim 75\% \) of the predicted value [7, 8], with a further 10–20% decrease in the supine position (15% representing twice the coefficient of variation of the measure that could be considered as the ULN) (figure 2) [8], while FRC and TLC are usually preserved in the seated position [7, 8], but are sometimes

| Respiratory muscle pressure assessment | Measured | LLN | ULN | Reference (mean value) | % of reference |
|---------------------------------------|----------|-----|-----|------------------------|---------------|
| MIP sustained for 1 s (at RV) \( \text{cmH}_2\text{O} \) | 68 | 80 | 168 | 124 | 55% |
| MIP at peak value (at RV) \( \text{cmH}_2\text{O} \) | 70 | | | | |
| MEP sustained for 1 s (at TLC) \( \text{cmH}_2\text{O} \) | 166 | 149 | 317 | 233 | 71% |
| MEP at peak value (at TLC) \( \text{cmH}_2\text{O} \) | | | | | |
| Maximum \( \text{SNIP cmH}_2\text{O} \) | 52 | 81 | 129 | 105 | 50% |

MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; SNIP: sniff nasal inspiratory pressure. *: reference values taken from [2, 3].

Figure 1 a) Maximal (outer black loop) and tidal (inner purple loop) flow–volume loops at rest in our patient. The predicted values loop is shown as a dashed profile. b) SNIP traces at rest in our patient. c) MIP traces at rest in our patient. Please refer to the text for more details.
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Figure 2: Current practice on the suspicion of respiratory muscle dysfunction (especially of the diaphragm), outside the intensive care setting. The figure describes how a clinician or physiologist suspects and treats respiratory muscle dysfunction (especially unilateral and bilateral diaphragm weakness), outside the intensive care setting. PImax: maximal inspiratory pressure; TF: thickening fraction of the diaphragm; PSG: polysomnography; CPAP: continuous positive airway pressure; NPPV: noninvasive positive pressure ventilation; PaCO2: arterial carbon dioxide tension; SaO2: arterial oxygen saturation measured by pulse oximetry. Please refer to the text for more details.

Reduced in severe cases [9]. In bilateral diaphragm weakness, VC usually reaches mean values of ~50% predicted and can further decrease by 30–50% when supine [10]. A normal supine VC makes the presence of clinically significant diaphragmatic weakness unlikely. TLC can also be reduced in the seated position (70–79% of the predicted value for mildly restriction and up to 30–50% of the predicted value in moderate-to-severe restriction) [9], while RV can be either increased or decreased or normal in the seated position (with a RV ranging from <50 to >150% predicted) [11]. Of note, the magnitude of the fall in VC in the supine position has been shown to be correlated to sniff Pal in this population [11]. The mechanism related to the reduction in supine VC is the cephalad displacement of abdominal contents in concert with ineffective activity of the accessory inspiratory muscles. A significant reduction in VC at diagnosis as well as its change or rate of decline over time are generally recognised as being among the criteria for initiating noninvasive ventilation [12, 13], and as being predictive of sleep disordered breathing, respiratory failure, progosis, evolution and response to treatment to a lesser extent in a wide range of neuromuscular disorders [14, 15], especially amyotrophic lateral sclerosis, with good sensitivity (80–95%) but variable specificity (50–90%) [16]. Conventionally, inspiratory and expiratory muscle strength has been evaluated by MIP and MEP at the mouth sustained for 1 s during a maximal static manoeuvre against a closed shutter [17]. However, MIP and MEP are volitional tests and are poorly reproducible with a coefficient of variation of ~25% [17]. A sniff manoeuvre is more natural and easier to perform. Pressure measured during sniff manoeuvres in the nostril (SNIP) are more reproducible and useful measures of global inspiratory muscle strength. Nevertheless, sniff manoeuvres are also effort-dependent tests and are difficult to interpret in ill or dyspnoeic patients performing submaximal efforts.

The gold standard method of evaluating the mechanical function of the major inspiratory muscles, i.e. the diaphragm, is measurement of the pressure generated by diaphragm contraction in response to phrenic nerve stimulation [17], during which this pressure can be assessed using the difference between the oesophageal and the gastric pressures (twitch Pdi). As mentioned previously, the best way to quantify diaphragm contractility is to monitor this pressure during a sniff manoeuvre (sniff Pdi) or during maximal inspiratory efforts against a closed airway (Pdi,max). On one hand these manoeuvres are largely effort dependent and are therefore variable. On the other hand, stimulation of the phrenic nerves generates a non-volitional contraction of the diaphragm. It is worth noting that while transcutaneous electrical phrenic nerve stimulation can be applied at the level of the neck (uni- or bilaterally), it has the disadvantage of being technically difficult in patients with obesity or anatomical variations of the phrenic nerve trajectories and is sometimes uncomfortable and painful. Magnetic stimulation of the phrenic nerves is less painful, can be applied bilaterally at the level of the cervical spine or uni or bilaterally at the neck, is reproducible in normal subjects [17] and is easy to perform. Overall, while phrenic nerve...
stimulation techniques are relatively easy tests that have been widely adopted for evaluating diaphragm function, they have the disadvantages of being time-consuming, of requiring considerable expertise and specialised equipment, and, as such, are poorly adapted to routine clinical practice [17]. Other novel means of evaluating diaphragm function will therefore be welcome.

**Points to emphasise**

An important point to emphasise is the absence of clearly defined lower limits of normality for measures of global inspiratory and specifically diaphragmatic strength. It has long been accepted that a MIP of >–80 cmH₂O in men and >–70 cmH₂O in women usually excludes clinically important inspiratory muscle weakness and that a normal MEP with a low MIP may suggest isolated diaphragmatic weakness. A more invasive, yet voluntary, measure used to estimate the strength of the diaphragm is the maximal transdiaphragmatic pressure (Pdi,max) obtained by inserting oesophageal and gastric balloon-catheters, with normal values widely ranging between 60 and 240 cmH₂O. It is generally accepted that absolute values of Pdi.max ≥80 cmH₂O in men and ≥70 cmH₂O in women are generally thought to exclude clinically significant diaphragm weakness. The Pdi measured during a sniff manoeuvre (sniff Pdi) also reflects diaphragm strength and may therefore represent an appealing alternative because it is much simpler to perform than Pdi,max. In clinical practice, sniff Pdi maximal values >100 cmH₂O in males and >80 cmH₂O in females are unlikely to be associated with clinically significant diaphragm weakness. Oesophageal pressure (Poes) or pressure measured in one nostril obtained during a sniff manoeuvre (sniff Poes and SNIP, respectively) reflect the integrated pressure of the inspiratory muscles on the lungs, and values numerically greater than >–70 cmH₂O in males or >–60 cmH₂O in females are also unlikely to be associated with significant inspiratory muscle weakness [17]. However, these measures are not specifically of diaphragm action but instead reflect the integrated pressure of all the inspiratory muscles involved in the sniff, therefore making it difficult to detect the presence of weakness of one or more of the inspiratory muscles. Generally, and broadly speaking, unilateral and bilateral diaphragm paralysis can be expected to decrease MIP or SNIP in the ranges of 60% [8] and <30% [10] of the predicted values, respectively (figure 2 and table 3). An important point to bear in mind is that the agreement between SNIP and MIP is variable; therefore, it has been suggested that these variables should be regarded as complementary and not interchangeable in the evaluation of inspiratory muscle weakness. MEP is generally preserved unless the underlying disease involves both the inspiratory and expiratory muscles (e.g. muscular dystrophy). It is worth noting that MEP may be found to be mildly reduced, in the range of 70–80% of the predicted value, simply due to a restriction-related reduction of TLC which may affect the optimal length–tension relationships of the expiratory muscles at that volume.

However, these values may be greatly impacted by the presence of underlying obstructive or restrictive lung disease [7] or obesity, especially if severe [18], and during acute exacerbations of the underlying disease, as is the case for chronic obstructive pulmonary disease (COPD) [19]. The case of COPD merits some clarification: the occurrence of progressive lung hyperinflation

| Table 3 Main differences between unilateral and bilateral diaphragmatic paralysis |
|---------------------------------|---------------------------------|
| **Symptoms**                    | **Bilateral diaphragmatic paralysis** |
| Usually asymptomatic            | Unexplained dyspnoea or recurrent respiratory failure |
| Possible dyspnoea on exertion and limited ability to exercise | Considerable dyspnoea at rest, when supine, or when immersed in water above their waist |
| Occasionally dyspnoea when supine | Fatigue, hypersomnia, depression, morning headaches and frequent nocturnal awakenings |
| **PFT**                         | **Subsegmental atelectasis and infections of the lower respiratory tract** |
| VC ∼75% predicted               | VC ∼50% predicted |
| VC ∼55–65% predicted when supine | VC ∼30–50% predicted when supine |
| FRC usually preserved           | TLC ∼70–79% predicted (mild restriction) |
| TLC usually preserved           | TLC ∼30–50% predicted (mildeto-severe restriction) |
| **RME**                         | **RV > predicted** |
| MIP ∼30–60% predicted           | MIP <30% predicted |
| SNIP ∼30–60% predicted          | SNIP <30% predicted |

Threshold values to suspect diaphragmatic weakness:
MIP or sniff Pdi or Pdi,max ≤80 cmH₂O in men, ≤70 cmH₂O in women
SNIP ≤70 cmH₂O in men, ≤60 cmH₂O in women

RME: respiratory muscles evaluation. Please refer to the text for more details.
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Self-evaluation questions

1. Concerning the evaluation of respiratory dysfunction of neuromuscular patients, which of the following is/are correct?
   a) The residual volume may be either increased or decreased or normal
   b) MIP decreases earlier than VC
   c) Night-time recording of transcutaneous carbon dioxide is useful for detecting nocturnal hypoventilation
   d) The reduction of VC in dorsal decubitus suggests diaphragmatic dysfunction
   
2. Regarding neuromuscular diseases, which of the following is correct?
   a) Dyspnoea is an early sign of hypoventilation
   b) Orthopnoea and poor sleep quality only appear in the very advanced stages
   c) A MIP of −80 cmH₂O in men and −70 cmH₂O in women usually excludes clinically important inspiratory muscle weakness
   d) TLC is always reduced
   e) None of the above

3. Which one of the following pulmonary function variables best reflects the strength of the diaphragm?
   a) MIP
   b) MEP
   c) FEV₁
   d) VC
   e) Peak expiratory flow

Key points

- Diaphragmatic dysfunction is an underdiagnosed cause of unexplained dyspnoea and should always be considered in the differential diagnosis of unexplained dyspnoea.
- Patients with unilateral diaphragmatic paralysis are usually asymptomatic but may have dyspnoea on exertion and limited ability to exercise.
- Once suspected, unilateral or bilateral diaphragmatic weakness can be evaluated using simple lung and respiratory muscle function tests, readily available in pulmonary function testing laboratories.
- The definitive diagnosis of diaphragm dysfunction can be obtained by phrenic nerve stimulation combined with diaphragmatic electromyography and/or twitch transdiaphragmatic pressure (twitch Pdi) measurement.
- However, these specific techniques require highly experienced physiology or ultrasonography specialists and may, therefore, not be available in some institutions or intensive care units. This may cause a significant delay in the diagnosis of these conditions.
- New approaches to provide simple, noninvasive, non-contact, early and easy-to-access procedures to diagnose diaphragmatic dysfunction are needed. Optoelectronic plethysmography, magnetic resonance imaging, respiratory muscle mechanomyogram and structured light plethysmography are promising new techniques.
significant delay in diagnosis of these conditions. As such, new approaches to provide simple, noninvasive and easy-to-access procedures to diagnose diaphragmatic dysfunction are needed. Optoelectronic plethysmography (OEP) is an established technique that allows measurement of the variations in the volume of the chest wall and its compartments during breathing [24, 25]. OEP has also been adopted to study several neuromuscular disorders [26–28]. Magnetic resonance imaging [29], ultrasonography [19, 30] and respiratory muscle mechanomyogram [31] are being increasingly used to evaluate an altered function of the diaphragm. Another emerging imaging tool is structured light plethysmography (SLP). SLP is a non-contact, noninvasive, easy to use method of assessment of breathing pattern and thoracoabdominal behaviour during spontaneous tidal breathing that allows the measurement of ventilatory activity through the stereoscopic analysis of respiratory-related distortions of a black and white checked pattern projected onto the chest wall and abdomen [32]. SLP has been validated in healthy subjects and in patients [32]. Further research is required to extend these observations, but these preliminary observations are promising.

Author contributions
All authors contributed to the content, writing and final approval of the manuscript.

Conflict of interest
P. Laveneziana reports personal fees from Novartis France and from Boehringer France, outside the submitted work. M-C. Niérat has nothing to disclose. A. LoMauro has nothing to disclose. A. Aliverti reports personal fees from Novartis France and from Boehringer France, outside the submitted work. M-C. Niérat has nothing to disclose. A. Aliverti reports personal fees from Novartis France and from Boehringer France, outside the submitted work.

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Suggested answers
1. a–d.
2. c.
3. a.

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