Diaphragm dysfunction: how to diagnose and how to treat?

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Shareable abstract (@ERSpublications)
Despite its clinical impact and advances in diagnostic tools, evaluation of diaphragmatic dysfunction remains inconsistent in many centres, highlighting the need for increased awareness to improve early detection and management https://bit.ly/4emhwI1

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Abstract

The diaphragm, crucial for respiratory function, is susceptible to dysfunction due to various pathologies that can affect the nervous system, neuromuscular junction or the muscle itself. Diaphragmatic dysfunction presents with symptoms ranging from exertional dyspnoea to respiratory failure, significantly impacting patients' quality of life. Diagnosis involves clinical evaluation complemented by imaging and pulmonary function tests. Chest radiography, fluoroscopy, and ultrasonography are pivotal in assessing diaphragmatic movement and excursion, offering varying sensitivities and specificities based on the type and severity of dysfunction. Ultrasonography emerges as a noninvasive bedside tool with high sensitivity and specificity, measuring diaphragm thickness, thickening fraction, and excursion, and enabling monitoring of disease progression and response to treatment over time.

Treatment strategies depend on the underlying aetiology and severity, ranging from conservative management to interventions such as surgical plication or diaphragmatic pacing. Ventilatory support, particularly noninvasive ventilation, plays a pivotal role in treatment, enhancing lung function and patient outcomes across unilateral and bilateral dysfunction.

Despite advances in diagnostic techniques, awareness and systematic evaluation of diaphragmatic function remain inconsistent across clinical settings. This review consolidates the current understanding of diaphragmatic dysfunction, highlighting diagnostic modalities and treatment options to facilitate early recognition and management of this entity.

Educational aims

- Understand the clinical impact of diaphragmatic dysfunction and recognise the main symptoms and signs that should raise clinical suspicion.
- Identify and differentiate the main aetiologies of diaphragmatic dysfunction, including neurological, neuromuscular and muscular causes.
- Learn the diagnostic work-up for diaphragmatic dysfunction, using the available diagnostic tools within each institution.
- Understand the various treatment strategies and their clinical applicability to enhance patient management.

Introduction

The diaphragm is a musculotendinous structure that separates the thoracic cavity from the abdominal cavity, playing a crucial role as the primary muscle involved in respiration. It has a dome-like shape and is covered by the pleura at the thoracic level and by the peritoneum at the abdominal surface. Structurally, it consists of a muscular portion, mainly peripheral and in contact with the ribs, and a tendinous portion, which is more central [1]. The region where the diaphragm abuts the lower thoracic wall is referred to as the zone of apposition.

Due to its crucial role in ventilation, accounting for up to 80% of the inspiratory work, the diaphragm has to be an extremely fatigue-resistant muscle [2]. This characteristic is attributed to its higher proportion of slow-twitch muscle fibres (type 1 – fatigue-resistant) compared with other skeletal muscles, which have more fast-twitch fibres (type 2 – glycolytic and more prone to fatigue). This composition enables the diaphragm to contract continuously throughout the day, including during sleep [3]. The rhythm of diaphragm contractions is regulated by its unique natural "pacemaker" located in the respiratory centre of the brainstem, making it the only skeletal muscle with this capability. The respiratory centre is controlled by neuronal interactions between the pons and medulla, which respond to afferent stimuli from chemoreceptors. The motor innervation of the diaphragm is provided by the phrenic nerve, which originates bilaterally from the cervical region at the roots of C3, C4 and C5 [4].

Pathologies that result in injuries to the central or peripheral nervous system, to the neuromuscular junction or within the diaphragmatic muscle itself can lead to loss of diaphragmatic function. Depending on the location and anatomical level of these insults, this loss of function can be more or less severe, with varying degrees of symptom severity [5]. Total loss of diaphragmatic function is referred to as diaphragmatic paralysis, which occurs, for example, in high spinal cord injuries. Partial loss of diaphragmatic function is termed diaphragmatic paresis, and is commonly seen in most neuromuscular diseases or other systemic conditions. Diaphragm dysfunction is a broad term that encompasses any level of impairment in the diaphragm's ability to contract and perform its essential respiratory functions [6].

Diaphragmatic dysfunction primarily manifests with respiratory symptoms, such as dyspnoea (during exertion or, in more severe cases, at rest), orthopnoea, sleep disordered breathing and hypersomnia [6]. Given the nonspecific nature of these symptoms, diaphragmatic dysfunction incidence is difficult to estimate, however, it is probably an underdiagnosed condition [7–9]. Nevertheless, it holds significant implications for patients' quality of life and, in severe cases, survival [10].

Despite the growing recognition of the clinical impact of diaphragm dysfunction, and the recent advances in diagnostic and treatment methods, it is not yet standard practice in many centres to assess diaphragmatic function and its potential contribution in patients with respiratory symptoms. Therefore, the aim of this review is to consolidate the main causes of diaphragmatic dysfunction and provide an update on the principal diagnostic and treatment modalities, aiming to raise awareness of this condition and improve its early detection and management.

Aetiology

Diaphragmatic dysfunction can have various causes; we have chosen to present these causes according to the anatomical level of involvement, classifying them into pathologies that affect the nervous system (central or peripheral), the neuromuscular junction or the muscular portion of the diaphragm (figure 1). However, it is important to note that in some cases, involvement may occur at more than one level (*e.g.* critical illness myopathy, where peripheral neuropathy and diaphragmatic myopathy coexist).

Nervous system

Central nervous system

Cerebrovascular accidents (ischaemic or haemorrhagic), depending on their location, can result in diaphragmatic dysfunction. It is postulated that hemidiaphragms are controlled by the contralateral motor cortex; thus, in the case of a stroke involving the cerebral cortex, the affected hemidiaphragm will be contralateral to the cerebral lesion, as observed with motor deficits in the rest of the body [11]. Catalá-Ripoll *et al.* [9] reported that 52% of patients with post-supratentorial stroke exhibited diaphragmatic dysfunction on the contralateral side of the lesion, with over half of these experiencing symptoms such as dyspnoea, orthopnoea or difficulty in mobilising sputum within the following 6 months. The latter is partly attributed to a reduced diaphragm excursion, which limits the positive pressure needed for effective coughing, along with expiratory muscle dysfunction and reduced cough reflexes [12]. Strokes or other lesions may also occur at the level of the internal capsule or brainstem, affecting ventilatory drive and automatic control of respiration, and therefore leading to diaphragmatic dysfunction. Examples of such insults include locked-in syndrome, Chiari malformation and syringomyelia [13–16].

Multiple sclerosis (MS) is characterised by the presence of demyelinating plaques on nerve fibres involving specific areas of the brain or spinal cord. When demyelination affects regions involved in producing or propagating nerve impulses to respiratory muscles, namely the diaphragm, respiratory muscle weakness starts to occur. In the early stages of MS, diaphragmatic dysfunction is rare but it becomes more frequent as the disease progresses, often after other respiratory muscles have already weakened. Therefore,

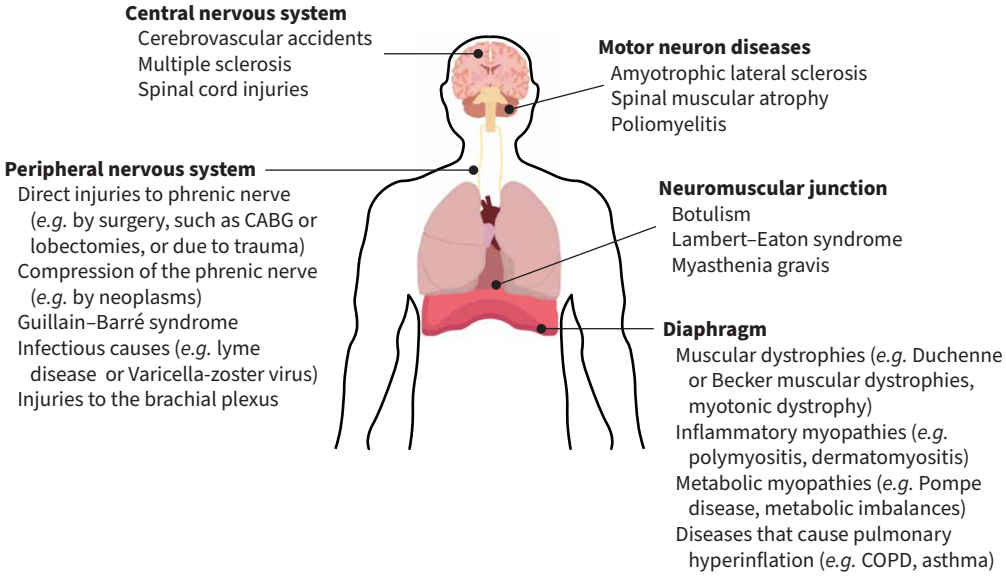

FIGURE 1 Causes of diaphragmatic dysfunction. CABG: coronary artery bypass graft.

patients with diaphragmatic dysfunction usually have advanced MS, often accompanied by bulbar dysfunction, impaired breathing control and other respiratory complications [17].

Parkinson disease (PD) is a neurodegenerative disorder caused by progressive dopamine loss in the substantia nigra, leading to motor symptoms such as tremor, bradykinesia and rigidity, and to non-motor symptoms, including autonomic dysfunction, sleep disturbances and respiratory problems. Respiratory dysfunction in PD, specifically diaphragmatic impairment, may result from multiple factors: restrictive dysfunction caused by rigidity and bradykinesia (which affect chest wall and diaphragm mobility), brainstem involvement (leading to dysfunction in medullary respiratory centres and central breathing control), and even PD medications like levodopa, which may induce diaphragmatic dyskinesias [18, 19].

Spinal cord injuries, with damage or even transection of the cervical spinal cord, are also important aetiologies of diaphragmatic dysfunction, as well as spondylolisthesis or other causes of compression of the cervical spinal cord. More cranial injuries (at the C1 or C2 levels) almost always result in diaphragmatic paralysis, whereas as we descend through the cervical spine, at the C3 to C5 levels, with involvement of the phrenic nerve roots, the likelihood of diaphragmatic dysfunction and the need for ventilatory support decreases [20].

Motor neuron diseases represent a group of progressive neurological disorders characterised by damage to neurons that control skeletal muscle activity, including the diaphragm, which leads to respiratory dysfunction. Conditions within this group include amyotrophic lateral sclerosis (ALS), spinal muscular atrophy and poliomyelitis. In poliomyelitis, patients may experience several years later (typically after a symptom-free interval of 15 years or more) progressive muscle weakness that can affect the diaphragm (post-polio syndrome) [21].

Peripheral nervous system

From its origin in the cervical spine down to the diaphragm, the phrenic nerve follows a relatively long trajectory, rendering it susceptible to injuries and damage caused by surgeries and trauma, which are the primary causes of nerve impairment. Cardiac surgeries often involve the use of thermal cardioplegia with ice slush and the dissection of anatomical structures near the phrenic nerve. This can result in nerve damage and diaphragmatic hemiparesis on the affected side in up to 60% of patients undergoing open-heart surgery, typically resolving spontaneously over time [22]. Furthermore, transection or compression of the phrenic nerve can occur during any surgery performed in the thorax, such as lung transplantation [23] or lobectomies [24], as well as traumas in this region [25].

The phrenic nerve can also be compressed by neoplastic processes, such as mediastinal masses, lung tumours, or neural-origin tumours like schwannomas [26–28]. Guillain–Barré syndrome can involve the

phrenic nerve through an immune-mediated process, leading to diaphragmatic dysfunction and respiratory failure requiring mechanical ventilation in up to 30% of cases [29]. Infectious causes (*e.g.* Lyme disease or Varicella-zoster virus infection) can, in severe cases, provoke phrenic nerve neuropathy and lead to respiratory failure [30, 31].

It is worth noting that injuries to the brachial plexus can also cause damage to the phrenic nerve, both due to the proximity of these nerve structures and the connection through fibrous tissue between them [32].

Neuromuscular junction

Diseases that impair the transmission of nervous stimuli at the neuromuscular junction can also cause diaphragmatic dysfunction. The most common mechanism involves the presence of antibodies targeting ionic channels or receptors involved in neurotransmission. The origin of these antibodies can be exogenous, as in the case of botulism, or endogenous, with the production of autoantibodies, as seen in Lambert–Eaton syndrome or myasthenia gravis [33]. In the latter, up to 20% of patients may experience a myasthenic crisis, during which diaphragmatic dysfunction can occur, with the need for ventilatory support [34].

Muscular system

Several myopathies can impair diaphragmatic function and lead to respiratory failure, including muscular dystrophies, inflammatory myopathies and myopathies of metabolic origin. Muscular dystrophies are a group of hereditary pathologies characterised by mutations in genes essential for muscle structure and function, resulting in skeletal muscle weakness with varying severity and progression rates. Involvement of respiratory muscles, including the diaphragm, occurs at variable stages of these diseases, but typically emerges after the loss of ambulation [35]. Metabolic myopathies are characterised by a dysfunction in muscle metabolism, leading to changes in energy production and its use by the muscles, including glycogen storage disorders (*e.g.* Pompe disease, McArdle disease), fatty acid oxidation disorders, disorders of purine metabolism or mitochondrial disorders [36]. Among these, ventilatory muscle weakness, including diaphragmatic dysfunction, is common in late-onset Pompe disease, with respiratory failure being a possible initial presentation [36].

The radius of diaphragm curvature is a key factor in its ability to contract effectively during inspiration. Conditions that cause diaphragm flattening and reduce this curvature radius place the muscle at a mechanical disadvantage, lowering its contraction capacity. This is observed in diseases that cause pulmonary hyperinflation, such as COPD and asthma, and is often underrecognised [37]. In addition, advanced-stage COPD patients often experience malnutrition and systemic inflammation with oxidative stress, which can further impair diaphragmatic function [38].

In critically ill patients, diaphragmatic dysfunction due to generalised myopathy is the primary cause of difficult weaning from mechanical ventilation, which leads to prolonged ventilation and increased muscle weakness, creating a vicious cycle [39]. Factors like malnutrition, steroid therapy and metabolic imbalances (*e.g.* hypophosphataemia, hypomagnesaemia and hypokalaemia) can also contribute to diaphragmatic dysfunction, especially when coexisting with other predisposing pathologies [10].

Acidosis, particularly acute respiratory acidosis, negatively impacts diaphragmatic function, primarily through decreased intracellular pH, which weakens diaphragmatic contractility and exacerbates muscle fatigue. Experimental studies suggest that acute respiratory acidosis significantly affects cross-bridges within muscle fibres, namely of the diaphragm, contributing to reduced respiratory efficiency [40].

Overall, the prognosis and natural history of diaphragmatic dysfunction depends on the underlying aetiology. It is important to note that the changes in the respiratory system associated with ageing, such as alterations in ventilatory drive, decreased muscle strength and reduced chest wall compliance, can also contribute to hypoventilation in these patients, and therefore should also be taken into account [41].

Diagnosis

The diagnostic suspicion of diaphragmatic dysfunction typically arises during the assessment of unexplained dyspnoea or following an incidental finding of diaphragmatic elevation in imaging studies. The diagnosis of this condition generally relies on clinical evaluation, imaging examinations and pulmonary function tests (using both noninvasive and invasive methods).

Clinical presentation

The symptoms reported by the patient and the severity of diaphragmatic dysfunction are determined by the anatomical level of the lesion and the presence of unilateral or bilateral involvement. Patients with

unilateral diaphragmatic dysfunction are predominantly asymptomatic, and complaints may arise in the presence of comorbidities such as obesity or cardiorespiratory diseases [42]. Common daytime symptoms in this situation include exertional dyspnoea and orthopnoea, and in some cases, hypoventilation, gastro-oesophageal reflux, cough or chest pain [43, 44]. Besides this, these patients may experience night-time symptoms, such as sleep disordered breathing, warranting a polysomnographic study to exclude and treat these problems if necessary [45–47].

By contrast, patients with bilateral diaphragmatic dysfunction frequently report daytime symptoms such as orthopnoea, intolerance to a supine position, exertional dyspnoea, and in severe cases, dyspnoea at rest [48]. Due to the absence of diaphragmatic function, these patients become highly dependent on accessory muscles of respiration, leading to dyspnoea during activities that involve the use of these muscles (*e.g.* raising arms above the head or lifting weights) [49, 50]. Specific situations, like immersion in water or bending over (antepnoea), also provoke dyspnoea due to the increased intra-abdominal pressure and passive displacement of the diaphragm into the thoracic cavity [49, 51]. In these patients, night-time symptoms also become more relevant, with sleep disordered breathing and hypoventilation posing significant issues, with complaints of frequent awakenings, nocturia, vivid nightmares, excessive daytime sleepiness and morning headaches [52, 53]. This is because, during sleep, especially during the REM (rapid eye movement) period, there is generalised muscle atony, and the main breathing muscle functioning is the diaphragm, leading to inevitable hypoventilation due to this muscle dysfunction [49, 54]. As a result, it is recommended that all these patients undergo polysomnography to identify sleep disorders [45, 47]. To prioritise patients, several questionnaires have been developed to identify the presence of respiratory sleep disorders in neuromuscular patients, one of them, the SiNQ-5, focuses on symptoms related to inspiratory muscle weakness, namely the diaphragm [55].

When patients present with symptoms suggestive of diaphragmatic dysfunction, clinicians should conduct a thorough physical examination to identify clinical signs that support this condition, namely evaluating the patient's respiratory pattern in the supine position, as this can reveal paradoxical thoracoabdominal breathing (figure 2) [50]. Physical examination in patients with unilateral diaphragmatic dysfunction is often nonspecific, with a possible decrease in respiratory sounds at the base of the affected hemithorax and dullness on percussion due to the elevation of abdominal organs. Conversely, patients with bilateral diaphragmatic dysfunction often exhibit a shallow breathing pattern characterised by rapid respiratory frequency and use of accessory respiratory muscles. Furthermore, when these patients are in the supine position, paradoxical thoracoabdominal breathing frequently occurs, raising the suspicion of diaphragmatic dysfunction [50].

Radiological diagnostic approaches

Chest radiography

Chest radiography is a simple examination that can raise the suspicion of a potential diaphragmatic dysfunction while simultaneously evaluating the lung parenchyma and other surrounding structures, to identify potential causes for diaphragmatic elevation [10]. When faced with a patient exhibiting diaphragmatic elevation on a chest radiograph, the initial step is to rule out causes leading to a decrease in lung volume on the affected side, which may mimic diaphragmatic dysfunction. Situations involving

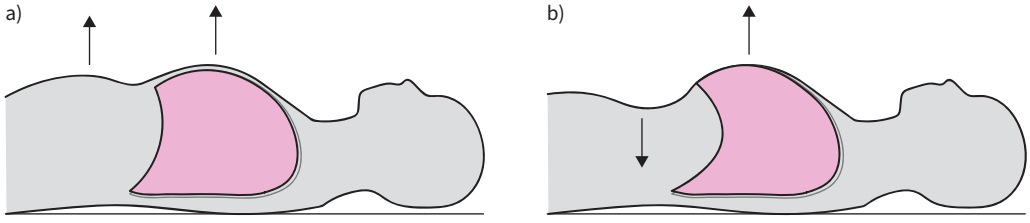

FIGURE 2 Paradoxical thoracoabdominal breathing. a) Diaphragm contracting normally during tidal breathing: with its contraction, the diaphragm moves caudally, increasing the abdominal pressure and reducing intrapleural pressure. Consequently, the abdomen moves outward and intra-alveolar pressure decreases, facilitating the influx of air that inflates the lungs. b) Dysfunction of the diaphragm: in cases of diaphragmatic dysfunction, the diaphragm loses the ability to contract during inspiration. Therefore, as the thoracic cage expands, the diaphragm moves cranially and abdominal pressure decreases, with an inward movement of the abdomen during thoracic cage expansion. This paradoxical abdominal movement is a characteristic observation during inspiratory phases in diaphragmatic dysfunction, particularly in the supine position.

increased intra-abdominal pressure or decreased lung volume, such as atelectasis, lobectomies or pulmonary fibrosis, should be considered [1]. For example, obese patients can present with an elevated right hemidiaphragm due to enlarged liver size, which is not related to diaphragm dysfunction, but can be encountered in clinical practice as obesity is common in Western societies.

In cases of unilateral diaphragmatic dysfunction, the sensitivity of chest radiography for diagnosis ranges from 67% to 90%, with a specificity of 44% [56, 57]. Despite this, in cases of unilateral involvement, chest radiography alone does not predict diaphragmatic function. In a cohort of patients where 64% were diagnosed with a hemidiaphragmatic elevation on chest radiography, unilateral diaphragmatic dysfunction was confirmed in only 24% through phrenic nerve stimulation [56].

In bilateral diaphragmatic dysfunction the sensitivity of chest radiography is lower, as the presence of elevated hemidiaphragms on both sides can be interpreted as weak inspiratory effort [1].

Fluoroscopy

Fluoroscopy is a simple imaging technique that allows for dynamic assessment of diaphragmatic excursion during regular ventilation and during the performance of respiratory manoeuvres, such as deep inspiration and the sniff test. In the absence of diaphragmatic disorders, it is expected that the diaphragm moves caudally during these manoeuvres. Therefore, to rule out the possible effect of gravity in the caudal movement, this examination should be performed in the supine position, and not in the sitting position. When there is diaphragmatic dysfunction, the affected hemidiaphragm either does not move or moves paradoxically in the cranial direction [1].

Diaphragmatic fluoroscopy is particularly useful in cases of suspected unilateral involvement, where the difference between the affected and normal hemidiaphragm is more easily observed, with a sensitivity for diagnosis of 90% [58]. However, it is not so valuable in patients with bilateral diaphragmatic dysfunction, where false negatives may occur. This happens because in some patients there is contraction of the abdominal muscles during expiration, followed by abrupt relaxation during inspiration, leading to a caudal movement of the diaphragm in the inspiratory phase that may mimic diaphragmatic contraction [5].

Ultrasonography

Ultrasound assessment of the diaphragm is a simple, bedside, noninvasive diagnostic method that is increasingly being used. The diaphragm is identified ultrasonographically by a three-layer structure, with two hyperechoic outer layers representing the pleural and peritoneal membranes, and the hypoechoic layer in the middle representing the diaphragmatic muscle [59].

Despite existing expert recommendations [60], there is currently no universally accepted protocol for diaphragm ultrasound assessment. Depending on the patient's position, measurements made by diaphragmatic ultrasound can vary; therefore, to minimise variability conducting all measurements in a consistent position is recommended [61]. When tolerated by the patient, the supine or semi-recumbent position is recommended by the authors, as it provides optimal and stable visualisation of the zone of apposition. It also enhances the accuracy and reliability of diaphragm assessments, with less variability and greater reproducibility, by maintaining a consistent acoustic window and reducing anatomical variability [62, 63].

For quantifying diaphragmatic function, several variables can be assessed through diaphragmatic ultrasound, the most commonly used are diaphragm thickness (Tdi), diaphragm thickening fraction (TFdi), and diaphragmatic excursion (EXdi). Tdi and TFdi should be evaluated using a high-frequency linear probe, in the zone of apposition, perpendicular to the chest wall. Tdi should be measured at the end of expiration, with its lower limit of normal being ~0.15 cm [64, 65]. However, this thickness is known to vary with posture and height, and it is not clear whether individuals with values below this truly have diaphragmatic dysfunction [61, 66, 67]. TFdi is calculated by measuring diaphragmatic thickness at end-inspiration and end-expiration and calculating the thickening fraction $((Tdi_{end\text{-}inspiration} - Tdi_{end\text{-}expiration})/Tdi_{end\text{-}expiration})$, with the lower limit of normal being 20% [65]. However, normative values for thickness and thickening fraction are challenging to establish due to variability in measurement techniques and patient comorbidities, such as COPD and obesity, which also impact the measurements [60]. TFdi correlates with the diaphragm's ability to contract and it can be used as a tool to help in ventilator weaning, as several studies have shown [68–70].

To evaluate EXdi, a curved or low-frequency probe is used in the subcostal region, between the anterior axillary line and mid-clavicular line, using the M-mode. This mode allows for the evaluation of the curve that describes diaphragm movement during tidal breathing and manoeuvres, such as deep inspiration and

the sniff test [57, 71]. During inspiration, the diaphragm moves towards the ultrasound probe, resulting in an upward curve, with a lower limit of normal for movement during deep breathing of 3.2 cm for women and 4.1 cm for men [72]. In the presence of diaphragm dysfunction, the diaphragm does not move or exhibits paradoxical movement, moving cranially, with a horizontal line or downward curve seen in the M-mode (supplementary video 1) [57].

The applications of diaphragm ultrasound are expanding, with studies demonstrating its utility in predicting ventilator weaning in intensive care unit patients [69, 70, 73], predicting prognosis in patients with acute exacerbations of COPD requiring noninvasive ventilation (NIV) [74, 75], and assessing diaphragmatic involvement in neuromuscular diseases [71, 76]. Consequently, and due to its increasing availability, this diagnostic method is being more widely adopted.

Nevertheless, this technique still has several limitations that should be kept in mind, namely its interobserver variability, the need for standardised protocols and adequate operator training [60]. Overall, the reproducibility of diaphragm ultrasound measurements for both excursion and thickness is generally regarded as good, with interobserver agreement correlation coefficients ranging from 0.56 to 0.989 [62]. However, operator skill is a significant factor, especially for the technically complex assessment of Tdi, which necessitates comprehensive training. However, the consistency of repeated measurements by the same operator is high, ensuring reliable follow-up examinations [60, 62, 77].

Physiological diagnostic approaches

Lung function tests

Pulmonary function tests are a widely available, noninvasive and easy-to-perform diagnostic method. In cases of diaphragmatic dysfunction, they allow for the quantification and understanding of its physiological impact, aiding in treatment decisions. When there is no confirmed diagnosis, these tests can provide data supporting or contradicting the diagnosis of diaphragm dysfunction and indicating its severity [78]. The main limitation associated with this diagnostic method is its dependence on patient cooperation [79].

Typically, patients with diaphragmatic dysfunction exhibit a restrictive ventilatory pattern, showing a decrease in vital capacity (VC) and, in severe cases, total lung capacity (TLC), while generally maintaining a normal diffusing capacity of the lung for carbon monoxide (D_{LCO}) [80]. In some cases, however, D_{LCO} may be reduced and the D_{LCO}/V_A ratio (D_{LCO} corrected for alveolar volume (V_A)) becomes a valuable tool in differentiating neuromuscular diseases with diaphragmatic dysfunction from other restrictive pulmonary diseases, namely interstitial lung diseases. In neuromuscular disorders that impact the diaphragm, D_{LCO}/V_A ratio often remains relatively normal, despite this D_{LCO} may appear reduced, since V_A is proportionately reduced due to restrictive patterns from weak inspiratory muscles [81].

The decrease in VC and TLC depends on the severity and laterality of dysfunction; however, these alterations can be found in various diseases affecting lung parenchyma and the thoracic cage, not being specific to diaphragmatic dysfunction. Nevertheless, the variation in VC with the decubitus position is more sensitive and specific for this diagnosis. A decline in VC with decubitus >25% has a sensitivity and specificity for the diagnosis of diaphragmatic dysfunction of 79% and 90%, respectively [78]. In cases of unilateral impairment, studies show a slight decrease in VC to ~70–80% of the predicted values, with a further drop of between 10% and 30% in the supine position [82]. However, in patients with bilateral diaphragmatic involvement, the decline in VC is more pronounced, potentially to 50% of the predicted values, with an even more significant decrease in the supine position (between 30% and 50% compared to sitting) [80].

In addition to assessing lung volumes, another way to evaluate diaphragmatic dysfunction and its severity is by measuring the pressures generated by this muscle contraction during inspiration, which can be done noninvasively or invasively.

Noninvasive assessments of diaphragmatic pressure

Noninvasive measurement of diaphragmatic muscle force involves quantifying pressures generated against a closed circuit during inspiration (maximal inspiratory pressure (MIP)) and expiration (maximal expiratory pressure (MEP)). These tests are easy to perform, well-tolerated and provide a quantitative assessment of respiratory muscle strength. However, they depend on patient cooperation and can be influenced by compensatory manoeuvres of thoracic and extrathoracic muscle groups [83]. Normal values for MIP are >80 cmH_2O in men and >70 cmH_2O in women, and typically in diaphragmatic dysfunction a decreased MIP with normal MEP can be found [83–85]. Based on these values, the ratio MEP/MIP was described, with a good correlation with VC variation with the supine position, making it particularly useful in patients unable to tolerate the supine position [79].

The sniff test can also be used to calculate the pressure generated by the respiratory muscles, particularly the diaphragm, through a rapid inspiratory movement through the nostrils – sniff nasal inspiratory pressure (SNIP). It is measured using a nasal catheter and is an easy manoeuvre that can be performed by patients unable to obtain a tight seal around the mouthpiece due to muscle weakness. Pressures >70 mmHg in men and >60 mmHg in women make diaphragmatic dysfunction unlikely [83].

Invasive assessments of diaphragmatic pressure

Invasive measurement of diaphragmatic pressure involves calculating transdiaphragmatic pressure (P_{di}), which is obtained by the difference between abdominal pressure and intrapleural pressure, estimated from probes placed in the stomach (P_{ga}) and oesophagus (P_{oes}), respectively ($P_{di}=P_{ga}–P_{oes}$) [83]. P_{di} values obtained depend heavily on patient cooperation and the use of accessory muscles, which can result in false-positive results for diaphragmatic dysfunction [86]. To overcome this limitation, P_{di} can be measured in response to phrenic nerve stimulation (twitch P_{di}), which does not require voluntary effort and is useful in cases where the patient cannot cooperate. Twitch P_{di} is the gold standard for assessing diaphragmatic function, allowing for quantification of diaphragmatic activity without interferences [83, 87]. Phrenic nerve stimulation is most commonly performed through transcutaneous electrical stimulation at the neck [83]; however, this technique (twitch P_{di}) is rarely used in clinical practice due to its invasive nature and associated discomfort, limiting its applicability to very specific situations [83, 86].

Treatment

General measures

In evaluating patients with diaphragmatic dysfunction, it is crucial to identify comorbidities that may exacerbate symptoms, such as obesity, respiratory or cardiovascular diseases, and address them. These patients should also undergo respiratory rehabilitation, particularly focusing on inspiratory muscle training, to regain diaphragmatic function as much as possible, thereby minimising the clinical consequences of diaphragmatic involvement. The benefits of inspiratory muscle training on diaphragmatic function have been demonstrated in patients with COPD [88], spinal cord injuries [89], and patients on mechanical ventilation [90]. Furthermore, in patients that underwent coronary artery bypass graft and had phrenic nerve injury, inspiratory muscle training also appeared to improve phrenic nerve recovery [91].

A lot of patients with diaphragmatic dysfunction are asymptomatic, without significant nocturnal hypoventilation, and in these cases, specific treatment is generally not required. In symptomatic patients, complaints depend on the laterality and severity of the impairment, and evolution depends on the aetiology. As previously described, there are reversible causes, namely metabolic causes (*e.g.* ionic or hormonal alterations), in which diaphragmatic weakness resolves with treatment (correction of ionic disturbances, replacement therapy with thyroid hormones) [92, 93], typically not necessitating specific treatment. There are also causes that resolve spontaneously over time, such as Guillain–Barré syndrome or infectious causes, for which an expectant approach is reasonable [29, 94]. However, if these situations present with severe symptoms or hypoventilation, temporary ventilatory support may be necessary until clinical improvement occurs.

Diaphragmatic plication

In symptomatic patients with unilateral diaphragmatic dysfunction, surgical plication of the affected hemidiaphragm is a procedure to consider. Its main objective is to reduce dyspnoea by immobilising the involved hemidiaphragm in a position of maximal inspiration, thereby decreasing its paradoxical movement [95]. Patel *et al.* [96] even demonstrated that the presence of paradoxical diaphragmatic movement is a good predictor of positive surgical outcomes, with improvements in lung function tests after surgery. Furthermore, this improvement in lung function was also shown by Welvaart *et al.* [97], demonstrating that plication leads to improved tidal volumes and reduced ventilatory frequency.

The procedure can be performed through various approaches, more or less invasive, each with its advantages and complications according to the clinical situation. One of the first approaches described was plication performed *via* thoracotomy, which showed improvement in symptoms and respiratory function tests after surgery. Subsequently, this technique evolved to become increasingly less invasive, and currently, it can be performed *via* thoracoscopy, with similar results which are maintained long-term [98]. The main disadvantage associated with the thoracic approach is that it requires single-lung ventilation, which may not be tolerated by patients with low respiratory reserve or poor functional status.

The alternative in these situations is the abdominal approach, which can also be performed *via* open surgery (laparotomy) or minimally invasive surgery (laparoscopy), with improvements demonstrated in dyspnoea reported by patients and respiratory function tests, and with the added benefit of allowing access

to both hemidiaphragms [98]. There are no comparative studies between the different plication techniques, but minimally invasive approaches are generally preferred due to their lower morbidity and the advantage of enabling early rehabilitation [98, 99].

The timing of plication is not fully defined, especially in cases where the causes may be reversible or where there may be some recovery of diaphragmatic function. Some studies suggest that after an observation period of ∼6–12 months or more, with optimisation of comorbidities and rehabilitation, if the dysfunction has not resolved, plication can be considered [100, 101]. In some cases of traumatic injury to the phrenic nerve, other studies state that patients should be observed for 1–2 years as the function of the affected nerve may improve over time [102]. Nevertheless, in severe cases of diaphragmatic dysfunction the observation period should be shorter and plication should be considered sooner [102].

In bilateral diaphragmatic dysfunction, plication is not usually indicated, although there are reports stating that it may be considered [103, 104]. However, this is not well established.

Diaphragmatic pacing

In selected cases of patients with bilateral diaphragmatic dysfunction, diaphragm pacing is a therapeutic option that consists of a device that electrically stimulates the phrenic nerve, resulting in diaphragmatic contraction and generation of breath [5]. It is necessary to demonstrate the integrity of electrical conduction in the phrenic nerve, and stimulation can be performed at cervical, thoracic or diaphragmatic level (on phrenic nerve insertion in the diaphragm), depending on the site of injury [105]. The primary goal of this therapy is to enable ventilator-dependent patients or those who do not tolerate continuous ventilation to have periods without the need for support [105].

The primary candidates for this therapy are patients with high cervical spinal cord injuries (above C3), with damage to the respiratory bulbospinal pathways but integrity of the phrenic nerve roots. In cases of lower cervical injuries, where there is involvement of the phrenic nerve roots, an alternative is direct diaphragmatic pacing stimulation [106]. In addition to spinal cord injuries, diaphragm pacing is also indicated in some central causes of hypoventilation, such as congenital central hypoventilation syndrome or syringomyelia [105]. Caution is needed in patients with unilateral diaphragmatic dysfunction, as it may cause ventilatory asynchrony.

Despite several studies and case reports describing its efficacy [107, 108], this treatment is not widely available and should be performed by experienced multidisciplinary teams.

Ventilatory support

Ventilatory support can be provided in the form of NIV or as invasive mechanical ventilation (in more severe cases of diaphragmatic dysfunction or when diseases progress and diaphragmatic function worsens meaning NIV is insufficient). Depending on the cause and severity of diaphragmatic dysfunction, the need for ventilatory support may be only during the night or permanent, requiring assistance 24 h a day [109]. The anticipated duration of ventilation also varies according to the pathology; for example, in patients with progressive neuromuscular diseases such as ALS, ventilatory support will be maintained until the end of life, whereas in iatrogenic or infectious causes, if there is recovery of diaphragmatic function, periods of ventilation may gradually be reduced until it is discontinued [110, 111].

The indications for initiating NIV in diaphragmatic dysfunction overlap with those for other neuromuscular or restrictive diseases, namely daytime hypercapnia (arterial carbon dioxide tension >45 mmHg) or nocturnal hypoventilation (S_{pO_2} <88% for >5 consecutive minutes) [110]. NIV is also indicated when the patient shows signs or complaints of night-time hypoventilation, orthopnoea or sleep disturbances due to REM sleep-related awakenings. In progressive neuromuscular diseases leading to diaphragmatic dysfunction, other indications for initiating ventilation include decreased MIP (<60% of predicted) or a decrease in forced vital capacity (FVC) or VC (<50% of predicted or <20 $mL \cdot kg^{-1}$, respectively) [110].

In terms of ventilatory parameters, there are limited published data, but bi-level pressure modes, volumetric modes or hybrids are typically reported, with specific settings varying from patient to patient [112–114]. In patients with neuromuscular diseases that involve pharyngeal/laryngeal muscles, concomitant obstructive sleep apnoea syndrome may occur, which must be taken into account when defining NIV settings [110].

Overall, the use of ventilatory support, particularly NIV, has been increasingly employed in patients with diaphragmatic dysfunction (both unilateral and bilateral). Studies demonstrate that prompt initiation of NIV when indicated improves lung function, quality of life and survival in these patients, contributing

significantly to patient outcomes [115, 116]. Its main advantages, compared to other treatments, are its noninvasive nature, wide availability, ease of use, reversibility, patient comfort and versatility in treating a broad range of conditions associated with diaphragm dysfunction.

Summary and future perspectives

Diaphragmatic dysfunction is an underrecognised cause of dyspnoea and respiratory failure, with significant clinical implications for quality of life and survival [10]. Its aetiology can originate from conditions affecting the nervous system, the neuromuscular junction or the diaphragm muscle itself, making it essential to understand the cause to determine the best management approach [5].

Diagnostic tools have advanced in this area, with diaphragmatic ultrasound emerging as a simple and widely available method that enables the evaluation and quantification of diaphragmatic function, as well as monitoring the progression of dysfunction in response to treatment [67–74]. Depending on the laterality and severity of symptoms, various treatments may be considered. In symptomatic patients, NIV is a safe and well-tolerated option with very favourable outcomes [112, 113].

Early recognition and multidisciplinary management are essential in optimising outcomes for patients with diaphragmatic dysfunction. Continued research and advancements in diagnostic tools and therapeutic interventions hold promise to optimise care and improve long-term prognosis in patients with diaphragmatic dysfunction.

Key points

- The severity and symptoms of diaphragmatic dysfunction vary based on the anatomical level of the lesion and whether it is unilateral or bilateral. Unilateral dysfunction is often asymptomatic or presents with mild symptoms such as exertional dyspnoea and orthopnoea. Patients with bilateral dysfunction frequently report dyspnoea with minimal exertion, orthopnoea and sleep disordered breathing. The prognosis and natural history of diaphragmatic dysfunction depends on the underlying aetiology.
- Diaphragmatic dysfunction is diagnosed through a combination of clinical evaluation, imaging (chest radiography, fluoroscopy, ultrasonography) and pulmonary function tests. Ultrasonography is particularly useful due to its noninvasive nature and high sensitivity and specificity, offering reliable and quantitative evaluations of diaphragm dysfunction at the bedside and enabling effective monitoring of disease progression.
- Management strategies include conservative measures, such as identifying and addressing comorbidities that can exacerbate the symptoms, and respiratory rehabilitation, particularly focusing on inspiratory muscle training. Surgical interventions, such as diaphragmatic plication and diaphragmatic pacing, are considered in severe cases. NIV has been increasingly employed due to its noninvasive nature and wide availability, allowing for improvements in lung function, quality of life and survival in these patients.
- Despite the increased availability of advanced diagnostic tools, systematic evaluation and awareness of diaphragmatic dysfunction remain inconsistent in clinical practice. Increased awareness is essential for early detection and effective management, which can significantly improve patient outcomes.

Self-evaluation questions

1. What is the most common initial symptom of diaphragmatic dysfunction?
    a) Chronic cough
    b) Exertional dyspnoea
    c) Chest pain
    d) Frequent infections
    e) Haemoptysis
2. Which of the following aetiologies is not usually associated with diaphragmatic dysfunction?
    a) Phrenic nerve injury
    b) Spinal cord injury at cervical level
    c) Critically illness myopathy
    d) Pulmonary embolism
    e) Guillain-Barré syndrome
3. Which diagnostic tool is most sensitive and specific for assessing diaphragmatic function?
    a) Chest radiography
    b) Fluoroscopy
    c) Pulmonary function tests
    d) Diaphragmatic ultrasound
    e) Computed tomography scan

4. Which of the following statements about the treatment of diaphragmatic dysfunction is true?
    a) Treating comorbidities, such as obesity and respiratory or cardiovascular diseases, and doing respiratory rehabilitation has no clinical impact on diaphragmatic dysfunction.
    b) Surgical plication is recommended for asymptomatic patients with unilateral diaphragmatic dysfunction to prevent paradoxical movement.
    c) Diaphragmatic pacing is typically used in patients with bilateral diaphragmatic dysfunction who have intact phrenic nerve function.
    d) NIV is only used in patients with unilateral diaphragmatic dysfunction.
    e) NIV is primarily used for temporary relief and is not suitable for long-term management.

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Suggested answers

1. b.
2. d.
3. d.
4. c.