The Diaphragmatic Dysfunction

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Paolo Formenti, Valentina De Giorgis,
and Davide Chiumello

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3.1 Introduction

Discontinuing mechanical ventilation is a key moment in the recovery of critically ill patients as it enhances the process of rehabilitation and reduces the morbidities associated (ventilator-induced lung injury—VILI, ventilator-induced diaphragm dysfunction—VIDD, ventilation-associated pneumonia—VAP) [1–3].

P. Formenti
Department of Anesthesia and Intensive Care, ASST Santi Paolo e Carlo, San Paolo University Hospital, Milan, Italy

V. De Giorgis
Department of Health Sciences, University of Milan, Milan, Italy

D. Chiumello (✉)
San Paolo Hospital, Intensive Therapy Department, University of Milan, Milan, Italy
e-mail: davide.chiumello@unimi.it

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Weaning from mechanical ventilation could be delayed by the combined actions of cardiovascular, abdominal, neuromuscular, and psychic pathologies [4].

3.2 The Diaphragm

The respiratory system is formed essentially by two components, the gas exchanger (the lung) and a mechanical pump that creates the in or out airflow from the lung (the thoracic cage and the associated muscles) [5]. These two components are interdependent and act in combination to allow a normal function of the respiratory system. The respiratory muscles are peculiar in comparison with the other muscles:

1. They are the unique skeletal muscles fundamental for life; in continuous contraction and so the most used skeletal muscles [6, 7];
2. They are under both voluntary and involuntary control;
3. They must face elastic and resistive loads, whereas the other skeletal muscles face mostly inertia [5].

Respiratory muscles represent only 3% of body weight but constitute a durable system with a strong functional reserve and a remarkable adaptation capacity to the pathophysiological requests of the organism.

3.3 Anatomy and Respiratory Function

The diaphragm is the main inspiratory muscle. It constitutes 0.5% of body weight in an adult norm type [8] with an area of 900 cm^2 [9, 10]. The phrenic nerve provides the motor innervation with fibers from C3, C4, C5; the sensory innervation related to the tendon center is afferent, as well to the phrenic nerve, whereas peripheral zones are afferent to intercostal nerves from T5 to T12. The diaphragm is a membranous muscle formed by a not contractile central area (the tendon center), which constitutes about 15/20% of its surface, and two muscle portions, the costal and crural diaphragm [11]. In humans, the fibers of the costal portion are inserted at the level of the xiphoid process of the sternum and the upper margins of the lower six ribs. From their insertions, the costal fibers run cranially in direct contact with the rib cage and they are apposed to the inner aspect of the lower rib cage.

On the contrary, the fibers of the crural portion are inserted at the level of the anterolateral portion of the first three lumbar vertebrae and on the aponeurotic arcuate ligament [12]. The ability of different portions of the muscle to generate force was studied through the evaluation of diaphragm regional thickness: one of the costal portions resulted in 40% higher cross-sectional area than the crural portion [13]. It is important to remember that there is a high regional difference in the same costal portion [14, 15]. Thus, we can observe an increasing thickness from the tendon center

toward the insertion [16]. We can state that there is no uniformity in the capacity of the diaphragmatic fibers to generate force. For instance, in a healthy human, an elliptical cylinder surmounted by a dome-shaped portion composes the overall shape of the diaphragm. The dome corresponds to the central tendon, while the cylinder portion is mostly formed by fibers in direct contact with the inner rib cage, the so-called zone of apposition (ZOA) [16, 17]. In adults in an upright position, ZOA represents about 30% of the surface of the rib cage. However, the shortening of fibers as a consequence of the diaphragmatic contraction reduces this component. This is equal to an average of 1.5 cm during normal breathing in a healthy human [12]. Therefore, as previously explained, the ZOA is the component that modifies its geometry much more while the dome has a caudal excursion, with relation to its rib insertions without a substantial modification in its shape and dimensions.

This pattern of contraction, actually similar to a piston inside a cylinder, shows a simplistic exemplification of the movement of the diaphragm during inspiratory breathing and its way to determine an increase in lung volumes.

3.4 Diaphragmatic Dysfunction and Fatigue

The diaphragm, like the other skeletal striated muscles, is subject to fatigue, so its capacity to manage heavy works under excessive strain is limited in time. However, it can tolerate resistive loads lower than 40% of the maximal load for an indefinite time [18]. The definition of diaphragmatic fatigue is the loss of capacity to produce a constant force with the repetition of action, reversible upon rest [19]. The etiology of muscle fatigue is due to a deficit of signal generation between the central nervous system and peripheral contractile system.

We can classify the respiratory muscles fatigue into three types:

- central fatigue,
- “high-frequency” peripheral fatigue
- “low-frequency” peripheral fatigue.

In central fatigue, the muscle’s capacity to produce force in repeated contractions is reduced due to nervous output reduction. Peripheral fatigue derives from the inability of the neuromuscular junction or the downstream portions to produce force in response to direct electrical stimulation, and it can be classified as “high frequency” or “low frequency” based on the force-frequency curve after fatigue. All these three processes can be active simultaneously in the presence of increased respiratory resistive load. The relative importance of each of them depends on how long the respiratory load is maintained and on other physiological variables such as the nutritional status, the arterial pressure, and respiratory gas exchange parameters. Fatigue is not a single event, but it is a process that occurs when the muscle is subject to an unsustainable load in time. A sequence of modifications takes place along the way from the generation of the signal to the production of force.

3.4.1 Diaphragmatic Dysfunction

The term "diaphragmatic dysfunction" refers to a range of clinical evidences ranging from partial deficit in generating force (weakness) to the total loss of diaphragmatic function (paralysis) [20, 21]. It is a condition often undiagnosed but that should be taken into account while approaching patients affected by dyspnea [22, 23]. There are conditions that predispose the development of this functional defect such as inflammatory or metabolic diseases, trauma and surgery, mechanical ventilation, mediastinal masses, myopathies, neuropathies, diseases that cause pulmonary hyperinflation [21, 24], involving the muscle unilaterally or bilaterally. Unilateral diaphragmatic dysfunction is not usually associated with symptoms at rest, while it may result in a reduction of exercise capacity or, rarely, causes orthopnea [25, 26]. Comorbidities such as obesity, neuromuscular degenerative diseases, cardiopathy, and/or pulmonary diseases can affect more extreme symptomatology. Bilateral diaphragmatic paralysis or a severe generalized muscle weakening is more commonly symptomatic. Patients can complain of dyspnea at rest or during exercise, orthopnea, fragmented or not restful sleeping due to nocturnal hypoventilation with consequent hypersomnia, depression, morning headache, and fatigue [27, 28]. Other complications are the development of subsegmentary atelectasis and lower respiratory tract infections [29].

In the Intensive Care Unit, common causes of diaphragmatic dysfunction and weakness are the critical illness polyneuropathy (CIP) and the myopathies [30], especially in patients with sepsis, multiorgan failure, hyperglycemia. These events should be regarded as potential causes of weaning failure.

Disuse atrophy can occur after a brief ventilation period or after curarization. It comes from atrophy of both fast- and slow-twitch muscle fibers. Moreover, malnutrition, dysoniae such as hypophosphatemia, hypomagnesemia, hypokalemia, hypocalcemia, thyroid dysfunction, and long-lasting dependence on mechanical ventilation are all predisposing factors communally present in ICU patients [31, 32]. The combination of a diaphragmatic weakness along with any process causing an increase in respiratory work (such as pneumonia, pulmonary edema, atelectasis, bronchospasm, pleural effusion) can exceed the contractile capacities of a weaker diaphragm and determine for the patient an extended period of mechanical ventilation. As far as the role of mechanical ventilation in the development of diaphragmatic dysfunction is concerned, the very existence of loss of ability to generate inspiratory force called "Ventilation-induced Diaphragmatic Dysfunction" (VIDD) is proved [33, 34]. This condition not only affects the diaphragm but also involves the rest of respiratory muscles [35, 36]. The pathophysiology of VIDD has been studied mainly in an animal model, although recently different studies have investigated this condition in humans, starting from brain-death donors [37], to ICU patients with different pathological conditions [38]. Other mechanisms seem to be involved in VIDD such as the reduction of diaphragmatic blood flow, the increase in oxidative stress, and the upregulation of cytokine cascades also active in sepsis (IL-6, TNF-α, IL-1β).

3.5 Invasive Evaluation of Diaphragmatic Function

Diaphragmatic function can be studied with different techniques divided into invasive and noninvasive. The currently available tools for invasive assessment of electrical activity of muscle are the diaphragm electromyography and the phrenic nerve stimulation; other less invasive technique are represented by the measurement of pleural and abdominal pressures, which allow to perform different variables such as the work of breathing (WOB), the transpulmonary pressure (Ptp), the transdiaphragmatic pressure (Pdi), and the esophageal and diaphragmatic pressure-time product (PTPes − PTPdi) [39]. Invasive methods also include those indices that can be derived directly from patients on mechanical ventilation, such as P0.1 and Pmusc index (PMI).

3.6 Noninvasive Evaluation of Diaphragmatic Function: The Ultrasound

Bedside ultrasound has become a routine device used in clinical practice in the Intensive Care Unit [40, 41]. The ultrasound examination of the diaphragm includes mainly two methods: the study of its excursion with the respiratory acts (displacement) [42, 43] and the evaluation of its thickness at ZOA [44, 45].

3.7 Diaphragmatic Displacement

The evaluation of diaphragmatic displacement requires the use of a convex 3.5–5 MHz probe, positioned at the subcostal level on the medium midclavicular line or anterior axillary line. The probe is directed medially, dorsally, and toward the subject's head in a way that the delivered ultrasound beam hits, with a straight angle, the posterior third of the hemi diaphragm under study (Fig. 3.1a, b). The procedure first involves the identification of a good-quality ultrasound image in bidimensional mode (B-mode) using the window provided by the liver on the right and by the spleen on the left (Fig. 3.1c). Once a good image is obtained, the M-mode is used in order to display the movement of the diaphragm along the exploration line, which must be perpendicular to the image of the diaphragm in B-mode. Tables 3.1 and 3.2 show the normal values for the displacement of right and left diaphragm, for men and women. During a normal respiratory act, the diaphragm moves in inspiration in a cranial–caudal direction, approaching the ultrasound probe positioned at the subcostal level, while in expiration, it moves away from the probe itself. Such displacements are visualized in M-mode as positive deflections in inhalation and negative deflections in exhalation. Further measurable parameters are the speed of shortening of the diaphragm (in cm/s), the time of inspiration (Tinsp, in seconds), and the total time of the respiratory cycle (Ttot, in seconds).

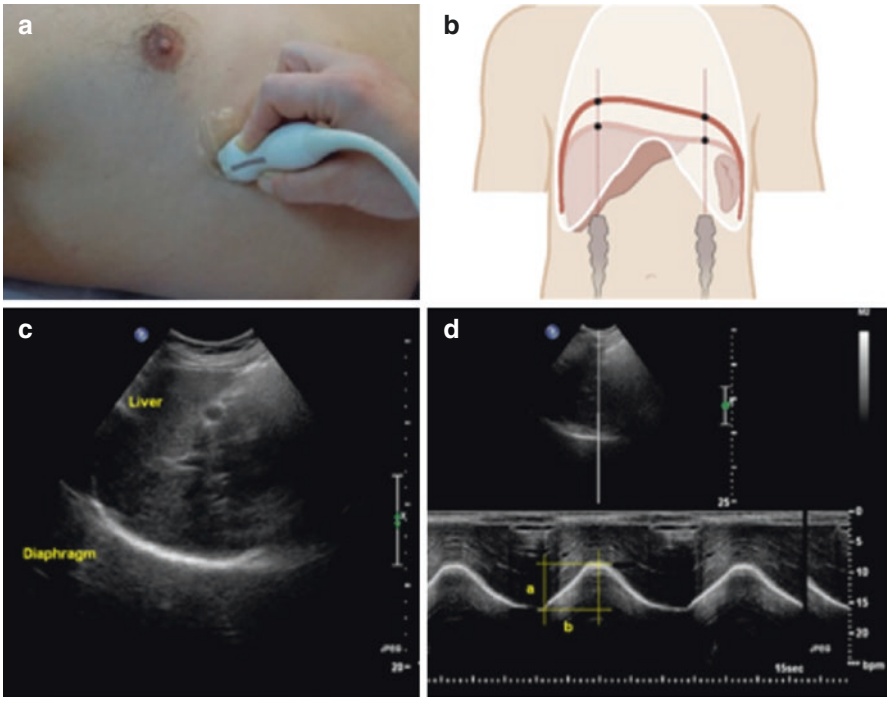

Fig. 3.1 Diaphragmatic displacement. (**a**) Ultrasound probe positioned at the left subcostal space to detect the diaphragm displacement. (**b**) Probe position allows a perpendicular projection of ultrasound using the hepatic and spleen acoustic windows. (**c**) B-mode ultrasound allows to detect the anatomical position of the diaphragm (hyperecogenic line) and the liver (**d**) M-mode view of diaphragm displacement

Table 3.1 Right diaphragmatic displacement values in male and female subjects

Variables	Male (cm)	Female (cm)	*P*
Quiet breathing	1.8 ± 0.3 (1.1–2.5)	1.6 ± 0.3 (1–2.2)	<0.001
Sniffing breathing	2.8 ± 0.6 (1.8–4.4)	2.6 ± 0.5 (1.6–3.6)	<0.001
Sigh	7 ± 1.1 (4.7–8.2)	5.7 ± 1 (3.6–7.7)	<0.001

Table 3.2 Left diaphragmatic displacement values in male and female subjects

Variables	Male (cm)	Female (cm)	*p*
Quiet breathing	1.8 ± 0.4 (1–2.6)	1.6 ± 0.4 (0.9–2.4)	0.002
Sniffing breathing	3.1 ± 0.6 (1.8–4.4)	2.7 ± 0.5 (1.7–3.7)	<0.001
Sigh	7 5 ± 0.9 (5.6–9.3)	6.4 ± 1 (4.3–8.4)	<0.01

3.7.1 Limits of the Technique

A clear limit is the presence of a bad acoustic window, which determines the acquisition of poor-quality images and difficult interpretation [42, 46, 47]. An additional limitation derives from the fact that the diaphragmatic displacement detected in patients during mechanical ventilation derives from the sum of the force generated by the diaphragm contraction and the one generated by the ventilator that causes a passive movement of the muscle. If the objective is to identify the ability to generate force in the absence of ventilator assistance, it will be necessary to record ultrasound images in spontaneous breath [48]. Umbrello et al. highlight the absence of a correlation between any other validated index that assesses the inhalation effort generated by the patient in assisted ventilation and the diaphragmatic displacement [49]. However, such limitation of use is not observed with the other fundamental ultrasound method during a single breath.

3.8 Thickness and Thickening Fraction

The other extensively used ultrasound method is the evaluation of the diaphragm thickness, which provides information on the contractile capacities of that muscle and the capacity to identify the presence of diaphragmatic paralysis [42]. The diaphragm thickness is measured using a linear probe at 7.5–10 MHz positioned at VIII-X intercostal space at the level of the anterior-midaxillary line oriented in a way that the ultrasound beam is parallel to the studied space (Fig. 3.2). The site allowing a more adequate assessment of diaphragmatic thickening (Tdi) is the ZOA where the muscle has a parallel course to the skin surface; therefore, the ultrasonographic beams cross it perpendicularly, in the absence of any distortion of the image. Thus, we can identify a three-band structure, two hyperechogenic ones, superficially the pleura and deeply the parietal peritoneum, between which appears a hypoechogenic structure that is the ultrasound image of the muscle belly (Fig. 3.3) [44, 50]. The positioning of the probe requires attention since the ultrasonographic beam must hit the diaphragmatic fibers perpendicularly.

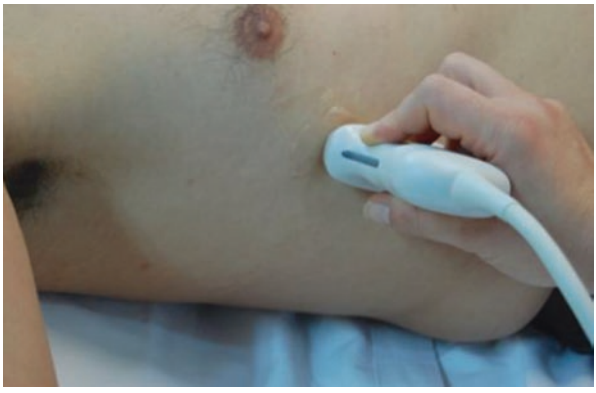

Fig. 3.2 Diaphragmatic thickness evaluation. The figure depicts the probe position on the right side to the detection of diaphragmatic thickness

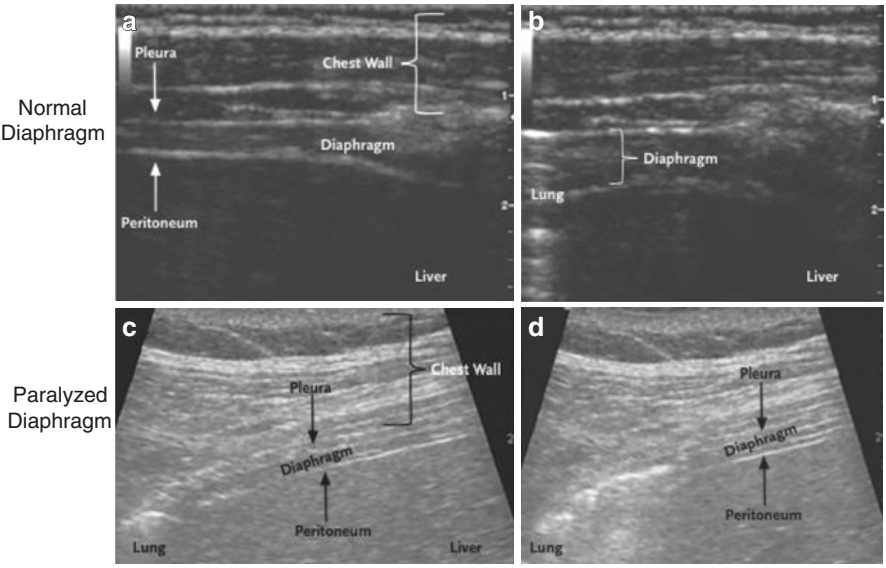

Fig. 3.3 Zone of apposition (ZOA) detected by ultrasound. The panels **a** and **b** detect a normal diagram contraction at end expiration; Panels **c** and **d** detect an example of diaphragmatic dysfunction

If there is a change of at least 5° of the angle of incidence, the two parallel hyperechogenic lines may appear distorted or be lost [51]. The rationale behind the evaluation of the diaphragm thickness lies in the fact that while the skeletal muscle contracts, its thickness necessarily increases since its volume remain constant. The same applies to the diaphragm. The contraction of the latter results in a reduction of the length of its fibers with a clear reduction of the total surface area, despite the insertion component of the muscle causing a simultaneous movement toward the outside of the lower ribs and thus an increase in the diameter of the rib cage [52]. Therefore, the mechanism of contraction of the diaphragm implies that its thickness has an inverse proportional relationship with the variations of length of the muscle fibers. A wide number of studies have tried to define a range of normality, taking measurement both in healthy subjects [51, 53, 54], in spontaneous breathing patients [55] and during noninvasive ventilation [56]. A clear evidence is given to an important variability of diaphragmatic thickness values, with a range at residual functional capacity (RFC) varying from 1.8 to 3 mm, and a progressive increase of the diaphragm thickness parallel to the increase of the lung volumes, up to an average increase of 54% (range: 42–78%) versus the total lung capacity. After obtaining the diaphragmatic thickness values at the expiration end and at the inspiration end, it is possible to evaluate the capacity of the diaphragm to thicken by calculating the "thickening fraction" (TF) evaluated in M mode at the level of the zone of apposition (Fig. 3.4) [56]:

$$\mathrm{TF} = \left(\frac{\text{Thickness at exhalation} \quad \text{Thickness at exp iration end}}{\text{Thickness at exp iration end}} \right) * 100$$

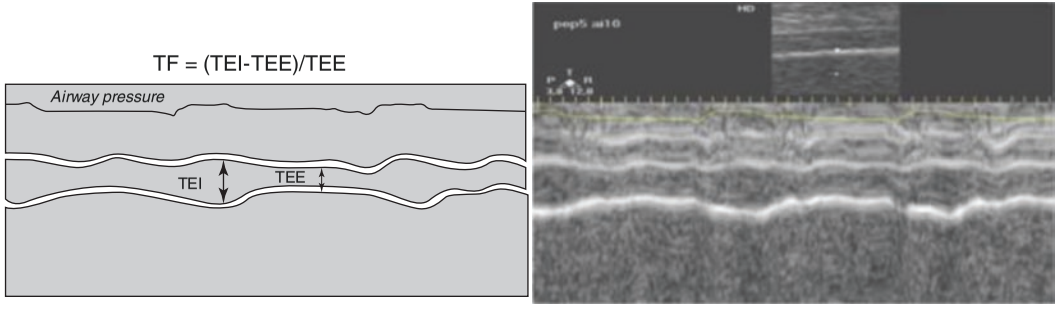

Fig. 3.4 Thickening fraction measurement. M-mode evaluation of the diaphragm to compute the thickening ratio (TF) between the end-inspiration thickness (TEI) and end-expiration thickness (TEE)

Gottesman and McCool have observed that in the presence of diaphragmatic paralysis, the diaphragmatic thickness is reduced to less than 2.0 mm—a value compatible with the development of atrophy in a chronically paralyzed diaphragm [42]. However, the only measurement of thickness may lead to false negatives in case of acute paralysis, or false positives based on the weight and height of the individual examined [57], from which derives the importance of the evaluation of the thickness of the diaphragm, being less than 20% in maximum breath in all subjects with diaphragmatic paralysis [42]. The diaphragm thickness finds increasing use as an index of weaning from mechanical ventilation [58] or recovery after muscular paralysis [59], thanks to the positive feedback obtained in several studies. Ferrari et al. [58] predictably showed TF as a parameter associated with success in trials in spontaneous breath**,** while Goligher et al. [60] suggested a determination of TF on at least two consecutive respiratory acts in order to achieve an increase in reproducibility in mechanically ventilated patients.

3.9 Conclusion

Currently, we have scientific evidence about how the contractile force of the diaphragm is affected by various factors and how these involve the development of diaphragmatic dysfunction in ICU patients. The correct balance between a protective ventilation strategy and the maintenance of a diaphragmatic activity is yet to be defined and represents a challenge for the clinical management of patients.

Definitely, the monitoring of diaphragm function should be implemented and considered in treatment algorithms in all mechanically ventilated patients. An optimal reference value for maximizing the inspiration effort has not yet been defined, and its use in the phases that follow the respiratory weaning could lead to creating new therapeutic models that are able to prevent and revert the process of diaphragmatic weakness.

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