

Diaphragm Dysfunction in Critical Illness



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The diaphragm is the major muscle of inspiration, and its function is critical for optimal respiration. Diaphragmatic failure has long been recognized as a major contributor to death in a variety of systemic neuromuscular disorders. More recently, it is increasingly apparent that diaphragm dysfunction is present in a high percentage of critically ill patients and is associated with increased morbidity and mortality. In these patients, diaphragm weakness is thought to develop from disuse secondary to ventilator-induced diaphragm inactivity and as a consequence of the effects of systemic inflammation, including sepsis. This form of critical illness-acquired diaphragm dysfunction impairs the ability of the respiratory pump to compensate for an increased respiratory workload due to lung injury and fluid overload, leading to sustained respiratory failure and death. This review examines the presentation, causes, consequences, diagnosis, and treatment of disorders that result in acquired diaphragm dysfunction during critical illness.

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Prevalence of Diaphragm Dysfunction in Mechanically Ventilated Patients

Over the past decade, considerable clinical effort and research has focused almost entirely on ICU-acquired limb muscle weakness, with little emphasis on the diaphragm. It has been suggested that this may be due to a lack of knowledge regarding the effects of critical illness on the respiratory muscles or the limited availability of tools to assess and monitor diaphragm function in patients in the ICU.^{1,2}

Multiple recent studies have shown, however, that severe ICU-acquired diaphragm

weakness develops in a large percentage of mechanically ventilated patients in the ICU.³⁻⁷ In many of these reports, objective nonvolitional measurements using the gold standard technique to assess diaphragm strength were used. Specifically, by assessing transdiaphragmatic twitch pressure (PdiTw) generated in response to bilateral anterior magnetic phrenic nerve stimulation (BAMPS), investigators report that mechanically ventilated patients in the ICU, on average, generate a PdiTw that is only 20% of normal.³⁻⁷ Although these represent average levels for mechanically ventilated patients, a high percentage of mechanically ventilated patients have far lower PdiTw

ABBREVIATIONS: BAMPS = bilateral anterior magnetic phrenic nerve stimulation; P₁₀₀ = negative airway pressure generated during the first 100 ms of an occluded inspiration; PdiTw = transdiaphragmatic twitch pressure generation; RSBI = rapid shallow breathing index; TF = thickening fraction; VIDD = ventilator-induced diaphragm dysfunction

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levels, which are indicative of more severe diaphragm weakness. For example, Supinski and Callahan⁶ found that 30% of patients had PdiTw levels < 5 cm H₂O, whereas only 6% of patients had PdiTw levels > 15 cm H₂O, values that are far less than those reported for normal healthy volunteers (eg, 28-38 cm H₂O).^{3,8} Additional studies have confirmed that on average, 60% to 80% of mechanically ventilated patients manifest clinically significant diaphragm dysfunction.^{9,10} Moreover, a recent study indicates that diaphragm weakness is present twice as often as limb weakness in critically ill patients.⁹

A Practical Approach to Recognition of Diaphragm Dysfunction in Critically Ill Patients

Unfortunately, despite the preponderance of evidence that respiratory muscle dysfunction is a common form of organ failure in critical illness and is associated with poor acute and long-term outcomes (discussed further on), clinicians frequently fail to consider this diagnosis. Theoretically, any patient who requires mechanical ventilation should be considered to be at risk for the development of diaphragm weakness. There are, however, several specific clinical scenarios that suggest the presence of diaphragm abnormalities. Although not intended to be comprehensive, the situations described further on may offer a practical approach to the recognition of diaphragm weakness in critically ill patients and can be easily detected at the bedside.

First, the presence of abdominal paradox, a marked inward motion of the abdomen during inspiration, is often a clue to the existence of severe diaphragm weakness or bilateral diaphragmatic paralysis.¹¹⁻¹⁴ In these patients, inspiratory contraction of the intercostal muscles “sucks” the flaccid diaphragm into the chest, resulting in an inward motion of the abdominal wall. In contrast, during inspiration in normal subjects, the active diaphragm moves downward and prevents inward motion of the abdomen. The clinical finding of abdominal paradox is most easily seen when patients are in the supine position; however, we have observed abdominal paradox during weaning trials or when patients are receiving low levels of pressure support, suggesting that diaphragm weakness may be present. There is, however, an important caveat to the consideration of abdominal paradox as a sign of diaphragm dysfunction. Pronounced expiratory muscle activation can induce diaphragm paradox in the absence of intrinsic diaphragm dysfunction; as a result, additional

testing is needed to confirm that true diaphragm weakness is present when this clinical sign is observed.

In addition, diaphragm dysfunction should be considered when a mechanically ventilated patient is making poor progress during weaning trials despite clinical improvements in pulmonary infiltrates, the lung examination, and several days of therapy (eg, administration of antibiotics or bronchodilators) to treat the underlying pulmonary disorder. The possibility of severe diaphragm weakness should also be entertained in patients with recurrent unexplained episodes of respiratory failure. Of course, undiagnosed coronary artery disease should also be a consideration for patients who present with this clinical phenotype.

It is also extremely useful to assess simple bedside indices of lung and respiratory system function (ie, respiratory system static compliance, inspiratory airway resistance, and the rapid shallow breathing index [RSBI])^{15,16} in mechanically ventilated patients who are not making adequate progress. A combination of relatively good lung mechanics but a high RSBI is a clue that respiratory muscle weakness may be present. As an example, one classic study¹⁷ found that patients with acid maltase deficiency-induced respiratory muscle weakness were commonly misdiagnosed with forms of intrinsic pulmonary diseases (eg, COPD) and that a correct diagnosis was achieved once objective testing was used to exclude other forms of respiratory failure.

The chest radiograph may also sometimes suggest the possibility of a significant diaphragm pathologic condition. Although not specific,¹⁸ unilateral or bilateral hemidiaphragm elevation can be seen with diaphragm paralysis or severe weakness, and this finding should prompt the use of simple tests (eg, diaphragm ultrasonography) to determine if diaphragm motion is adequate (see the sections on diagnosis further on).

A final clinical situation that warrants consideration of severe diaphragm dysfunction is patients who have no prior history of lung disease who present with hypercapneic respiratory failure and a normal chest radiograph. In these instances, patients may have pre-existing undiagnosed primary neuromyopathic processes, such as amyotrophic lateral sclerosis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, carnitine deficiency, Pompe disease, polymyositis, or inclusion body myositis.^{12,18-22} Although there can be considerable heterogeneity in the presentation of many of these disorders, as well as marked variation in the

severity of dysfunction from muscle to muscle, in some patients, acute respiratory failure due to respiratory muscle weakness may be the major presenting component of these diseases. Neurologic consultation is required for such patients. Several of these disorders are eminently treatable, and failure to diagnose these conditions represents a lost opportunity.

Consequences of Acquired Diaphragm Weakness in Mechanically Ventilated Patients

Although many practitioners assume that ICU-acquired diaphragm weakness is transient and does not directly affect patient outcomes, there are several recent studies indicating that diaphragm strength is a major determinant of both the time required to wean patients from mechanical ventilation and ICU mortality.^{6,23}

Specifically, one study found that the average duration of mechanical ventilation was only 5.5 ± 2.0 days for stronger patients (as defined by a PdiTw > 10 cm H₂O) but increased to 12.3 ± 1.7 days for patients with a PdiTw < 10 cm H₂O ($P < .02$ compared with PdiTw > 10 cm H₂O).⁶ At extremely low levels of diaphragm strength (eg, PdiTw < 4 cm H₂O), duration of mechanical ventilation increased further in this study, with most of these patients requiring more than 3 weeks to wean from mechanical ventilation.⁶

Diaphragm weakness has also been shown to correlate with higher mortality. Specifically, in one study, the incidence of ICU death was 49% in the patients with the weakest diaphragms (ie, with PdiTw < 10 cm H₂O) but only 7% for patient with stronger diaphragms (PdiTw levels > 10 cm H₂O; $P = .022$).⁶ In fact, it has been reported that diaphragm weakness is a far stronger predictor of ICU mortality than the degree of organ failure, severity of lung function abnormalities, age, sex, steroid use, or the comorbidity index in mechanically ventilated patients.²⁴ There are several potential explanations for the association of mortality and diaphragm weakness. In some instances, sicker patients are more likely to have illnesses (eg, sepsis) that both increase mortality (eg, shock) and lead to the use of ventilator settings that engender diaphragm weakness. As a result, in some cases, it could be argued that death may be due to the underlying disease process and that diaphragm weakness may represent an epiphenomenon. In other cases, however, patients requiring sustained mechanical ventilation may have care withdrawn when it proves difficult to wean these patients from the ventilator.^{6,24} A recent analysis suggests that diaphragm

weakness may be the main factor preventing liberation from mechanical ventilation in many of these patients; for this subgroup, it is likely that diaphragm weakness is causally related to death.^{6,24} Additional work will be needed to confirm these results and fully assess the mechanisms and implications of these previous findings.

Causes of Diaphragm Dysfunction in Mechanically Ventilated Patients

When diaphragm weakness is found in mechanically ventilated patients, it is always important to first exclude the presence of easily treatable endocrine and electrolyte disorders such as hypophosphatemia, hypomagnesemia, and hypocalcemia.²⁵ Severe diaphragm dysfunction can be present in hypothyroidism, and sometimes the major manifestation of this disease may be respiratory failure due to respiratory muscle weakness.²⁶ Prolonged hyperglycemia, profound malnutrition, severe untreated renal failure, use of neuromuscular blocking agents, and sustained administration of high doses of corticosteroids may well contribute to reduced muscle strength in a subgroup of mechanically ventilated patients in the ICU.

The majority of diaphragm weakness in patients in the ICU, however, is not the consequence of easily treatable conditions. In many cases, diaphragm dysfunction is thought to occur primarily as a consequence of mechanical ventilation per se (ventilator-induced diaphragm dysfunction [VIDD]). There is also strong evidence that processes other than VIDD, including sepsis and other systemic infections are responsible for many cases of ICU-acquired diaphragm weakness. These two conditions will be discussed in more detail further on.

Ventilator-Induced Diaphragm Dysfunction

Ventilator-induced diaphragm dysfunction is the loss of diaphragm force-generating capacity that is specifically caused by the use of mechanical ventilation.²⁷ The recent recognition that mechanical ventilation can induce diaphragm atrophy was convincingly made in animal studies. In one of these studies, Powers et al²⁸ reported that rats rapidly developed progressive diaphragm atrophy and loss of diaphragm force-generating capacity when mechanically ventilated using controlled mechanical ventilation (Fig 1A). In this study, electromyography confirmed complete diaphragm inactivity, which was accomplished by using heavy levels of sedation. Subsequently, a series of patient studies provided evidence that ventilator-induced diaphragm atrophy also develops in patients undergoing mechanical ventilation. In one of these, Levine et al²⁹ reported that

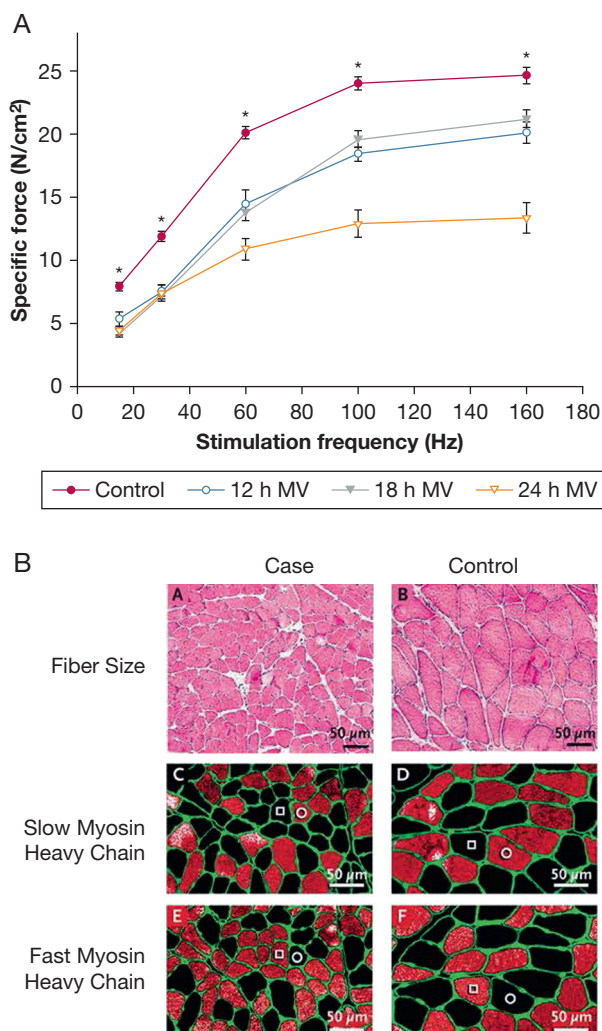


Figure 1 – Effect of mechanical ventilation on the diaphragm. A, *In vitro* force–frequency relationships in diaphragms from rats undergoing mechanical ventilation (MV). As shown, MV induced significant ($P < .05$) and progressive reductions in the diaphragm specific force-generating capacity (force/cross-sectional area) when compared with control animals. B, Comparison of a representative diaphragm biopsy specimen from a mechanically ventilated brain-dead organ donor (case subject) and a control patient undergoing surgery and mechanical ventilation for 2 to 3 hours. As shown, diaphragm fiber size was reduced in the case subject, affecting both slow and fast twitch fibers, indicating that prolonged controlled mechanical ventilation induces diaphragm fiber atrophy in humans. (Reprinted with permission from Powers et al.²⁸ and Levine et al.²⁹)

mechanically ventilated brain-dead organ donors rapidly experience severe diaphragm atrophy (Fig 1B). In an earlier postmortem study, Knisely et al³⁰ found decreased diaphragmatic muscle mass and myofiber atrophy in infants and neonates who received long-term ventilatory assistance. A number of additional human studies, performed primarily in brain-dead organ donors, have since provided more evidence that diaphragm atrophy develops in patients who receive prolonged mechanical ventilation.^{31,32}

To delineate the cellular mechanisms by which mechanical ventilation per se induces diaphragm atrophy and weakness, a number of elegant animal studies have shown that VIDD is associated with oxidative stress, activation of several proteolytic pathways (caspases, calpains, and the ubiquitin-proteasomal system), and mitochondrial dysfunction within the diaphragm, which induce loss of muscle size and strength.^{28,33-40} Additional studies suggest that ryanodine receptor dysfunction contributes to the pathology of VIDD³⁵ and that activation of autophagy during VIDD provides a protective role.⁴¹ More recently, a number of studies have examined diaphragm tissues from patients undergoing prolonged mechanical ventilation and verified many of the findings observed previously in animal studies, largely confirming that the same pathophysiological processes occur in patients with little or no respiratory drive undergoing mechanical ventilation.^{27,31,32}

There are several caveats, however, about the VIDD syndrome. First, VIDD is a diagnosis of exclusion,²⁷ and it should not be assumed that all mechanically ventilated patients have weakness by this mechanism. Second, although animal studies indicate it is easy to induce diaphragm weakness when the respiratory drive to this muscle is ablated by sedation and high levels of mechanical ventilation, VIDD does not occur when animals are allowed to intermittently activate the diaphragm during mechanical ventilation.^{42,43} This work also indicates that VIDD is rapidly reversible once animals are removed from mechanical ventilation and allowed to breathe spontaneously, with both diaphragm atrophy and weakness rapidly restored to normal within a few hours.⁴⁴ As a result, if VIDD per se was largely responsible for ICU-acquired diaphragm weakness, this problem should, in theory, be easily treated simply by gradually reducing the level of ventilator support (eg, with pressure support ventilation) over a relatively short period (hours).⁴⁵ This rapid reversibility has never been shown to occur in critically ill patients, arguing that other mechanisms of diaphragm weakness and respiratory failure play a role in patients who are difficult to wean from mechanical ventilation.

Infection-Induced Diaphragm Dysfunction

The other potential contributor to the development of diaphragm weakness in mechanically ventilated patients is infection. Two clinical studies have suggested that infection is a major risk factor for the development of severe diaphragm weakness in critically ill mechanically

ventilated patients.^{6,7} One of these studies reported that infected mechanically ventilated medical patients in the ICU had a median PdiTw of only 5.5 cm H₂O (25%-75% confidence levels of 4.0-7.9 cm H₂O), whereas uninfected patients had a median PdiTw of 13.0 cm H₂O (25%-75% confidence levels of 11.0-14.7; $P < .001$)⁶ (Fig 2B). In a second report, Demoule et al⁷ found a similar relationship in a study of mechanically ventilated patients, with diaphragm strength for infected patients approximately half that of uninfected individuals. Although a more recent study has disputed this relationship,⁹ this latter work used techniques to assess diaphragm strength that may have been suboptimal.⁴⁶

Further evidence for a causative relationship between infection and diaphragm weakness is derived from numerous basic science animal experiments that have shown that infections severely reduce diaphragm strength. These studies have demonstrated that acute infection reduces diaphragm strength by as much as 80% within 24 hours^{47,48} (Fig 2A). Pathophysiological mechanisms identified as responsible for these rapid and dramatic reductions in diaphragm force-generating capacity include activation of proteolytic pathways, including calpains, caspases, and the proteasomes.⁴⁹⁻⁵¹ Recent work suggests that infection produces these effects by eliciting cytokine production, with cytokines in turn leading to activation of cell-surface neutral sphingomyelinase receptors.^{47,52} Activation of these receptors produces alterations in muscle ceramide metabolism, stimulating mitochondrial free radical generation and inducing cellular oxidative stress.⁵² Oxidative stress damages mitochondrial electron transport chain subunits,⁵³ contributing to reductions in muscle endurance, and also activates proteolytic enzyme pathways, leading to reductions in contractile proteins⁵⁴ and reductions in muscle strength.

Diagnostic Techniques: Use of Ultrasonography to Assess Diaphragm Dysfunction in Mechanically Ventilated Patients

Recently, ultrasonography has emerged as a tool for assessing the diaphragm in mechanically ventilated patients. This technique is attractive because it is noninvasive, the equipment is readily available in most ICUs, and serial assessments can be performed easily compared with the technically challenging methods used for transdiaphragmatic pressure measurements (discussed in the following section). The usual approach

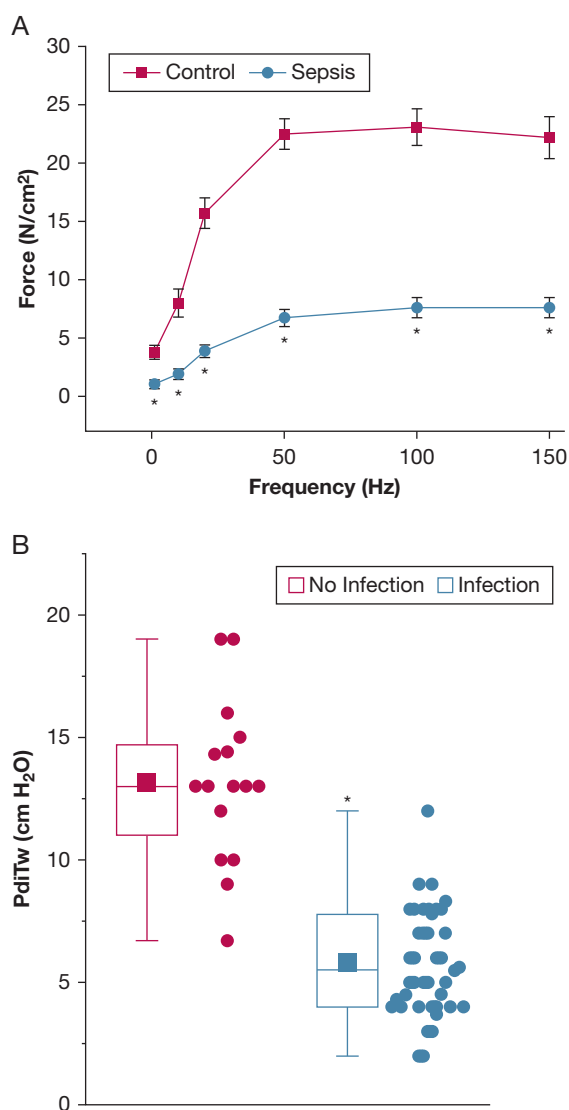


Figure 2 – Effect of infection on diaphragm function. A, In vitro force-frequency relationships for control and septic mice. Sepsis was induced with cecal ligation puncture; control mice were animals who were operated on and underwent the same protocol without ligating the cecum or performing puncture and evaluated 24 hours later. As shown, sepsis induced marked reductions in the diaphragm specific force generation (force per cross-sectional area) ($P < .001$ for all comparisons). B, Transdiaphragmatic twitch pressure (PdiTw) measurements in 57 critically ill mechanically ventilated patients. Patients were classified as uninfected or infected on the basis of whether they were actively receiving treatment for an infection. Data from individual patients are shown for each group on the right, whereas plots on the left for each group show mean (filled squares), median levels (middle line of box), 25% and 75% confidence intervals (upper and lower borders of the box), and 1% and 99% intervals (whiskers above and below the box). Infection was associated with significant lower PdiTw values; *, statistical significance). (Adapted with permission from Supinski and Callahan⁶ and Supinski et al.⁴⁷)

to diaphragm ultrasonography involves placing the patient in the supine position, as this offers ease of use in critically sick patients, less overall variability, less side to side variability, and greater reproducibility.^{55,56}

However, optimal diaphragm ultrasonography involves measuring indices during spontaneous respiration and off mechanical ventilation. Assessments while on mechanical ventilation result in greater difficulties when interpreting results, especially when the patient is sedated and on full ventilator support mode. The appropriate manner in which diaphragm ultrasonography should be used during mechanical ventilation to detect diaphragm dysfunction, predict extubation success or failure, monitor respiratory workload, and assess atrophy is currently under active investigation.⁵⁷⁻⁶⁰

In general, there are two major forms of ultrasonographic assessment of the diaphragm: determination of diaphragm excursion and measurement of diaphragm thickening. Diaphragm excursion is obtained using the liver or spleen as an acoustic window, with a low-frequency curvilinear or phased-array transducer (1-5 MHz) using two-dimensional brightness or B-mode ultrasonography, and M mode ultrasonography.⁵⁵ The right side of the diaphragm is examined from the anterior subcostal view by positioning the probe below the right costal margin between the midclavicular and anterior axillary lines (Fig 3A). The left side of the diaphragm is studied from a low intercostal or subcostal approach in which the probe is positioned between the midaxillary and anterior axillary lines.⁶¹ The probe is angled cranially so that the ultrasound beam reaches perpendicular to the posterior part of the diaphragm⁶¹ (Fig 3B). The ultrasonographic appearance of the diaphragm is seen as a single thick echogenic line (Fig 3C). In the M mode, all the reflectors along the ultrasound line are displayed along the time axis, and the signal amplitude is displayed as a function of time, allowing for quantification of motion (Fig 3D). The direction of diaphragm movement toward the transducer (positive deflection on M mode) or away from the transducer (negative deflection on M mode) can be correlated with the phases of respiratory cycle.^{55,56,61} Normal ranges of diaphragmatic excursion from the resting expiratory position to deep inspiration have been reported in adults to be 0.9 to 9 cm, with higher values in men and progressively higher values reported with deep breathing over sniffing over quiet breathing.⁶¹ Diaphragm paralysis is indicated by absence of excursion with quiet breathing and deep breathing and with absence of movement or with paradoxical movement either with normal breathing or with sniffing^{55,60} (Fig 4). Similarly, diaphragm weakness is suggested by less than normal amplitude of excursion on

deep breathing and with or without paradoxical movement on sniffing.^{56,60}

Thickness assessment of the diaphragm can be obtained at the zone of apposition on an intercostal view using two-dimensional B-mode and M-mode ultrasonography and requires a high-frequency linear-array probe (6-13 MHz). The transducer is positioned at the midaxillary line at the intercostal space between the seventh and eighth ribs or the eighth and ninth ribs to obtain an ultrasonographic image in the sagittal plane^{55,62} (Fig 5A). The ultrasonographic appearance of the diaphragm in the zone of apposition is usually seen as a three-layered structure composed of two parallel echogenic layers of diaphragmatic pleura and peritoneal membranes sandwiching a nonechogenic layer of muscle (Fig 5C). Thickening fraction (TF) can be calculated using the M mode in the zone of apposition: $TF = (\text{thickness at end inspiration} - \text{thickness at end expiration}) / \text{thickness at end expiration}$ ⁶⁰ (Fig 5D).

As an example of the utility of diaphragm ultrasonographic measurements, a recent report of serial diaphragmatic ultrasonographic assessments in 107 mechanically ventilated patients showed that over the first week of mechanical ventilation, diaphragm thickness decreased by more than 10% in 47 patients (44%), increased by more than 10% in 13 patients (12%), and was unchanged in 47 patients (44%).⁶³ In this study, the loss of diaphragm thickness was associated with a lower degree of diaphragm shortening, which may represent a reduction in diaphragm activation while receiving mechanical ventilatory support. Importantly, although there were no appreciable outcome differences across these three groups of patients, this study shows that the diaphragm undergoes detectable changes by ultrasonography during mechanical ventilation, leading the authors to suggest that titration of ventilatory support to maintain an adequate level of diaphragm activity may prevent diaphragm atrophy.⁶³

Although ultrasonography is an evolving technique in the ICU setting and is widely accepted as a tool for assessing the diaphragm in mechanically ventilated patients, there are important limitations to its use. First, ultrasonographic image acquisition and analysis is operator dependent and requires training.^{57,64,65} A recent review suggests that to ensure accuracy and reproducibility of the TF requires significantly more training than that required to assess excursion.⁵⁷ Moreover, successful visualization can be improved by a thorough understanding of lung artifacts, as well as the

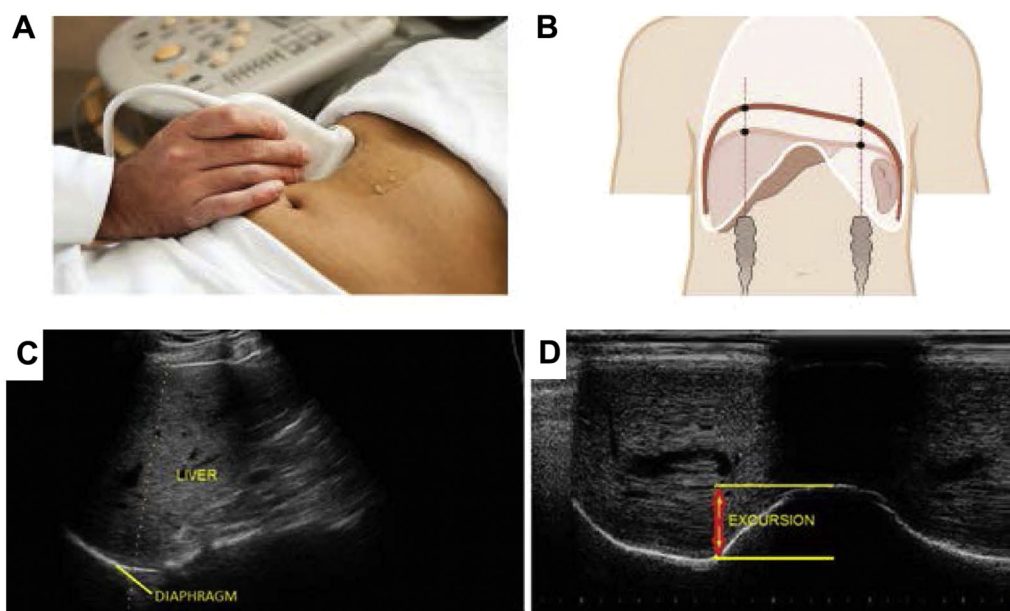


Figure 3 – Diaphragm excursion. A, Appropriate probe position for B- and M-mode diaphragmatic excursion measurements using a 1- to 5-MHz probe. B, Path of the ultrasound beam as it travels to image the diaphragm. C, B-mode diaphragm ultrasonography; the bright line reflects the diaphragm using the anterior subcostal approach. D, M-mode tracing showing the amplitude of excursion during deep breathing. The arrows indicate the beginning and end of diaphragmatic contraction, and the distance between the arrows indicate diaphragm displacement (excursion). (Adapted with permission from Sarwal et al⁵⁵ and Zambon et al⁵⁷).

use of correct techniques and patient positioning. In several reports, particularly in mechanically ventilated patients, technical difficulties encountered with examination of the left hemidiaphragm have led investigators to limit assessments to the right hemidiaphragm.^{63,64,66}

Second, the degree of shortening of the diaphragm during contraction is strongly influenced by the level of diaphragm motor outflow, which varies tremendously in mechanically ventilated patients as a function of the degree of sedation. It is difficult to control for this

variable in general, and “complete” control of this factor would require the use of controlled activation of the diaphragm, that is, the use of exogenous electrical or magnetic activation of the diaphragm. In addition, diaphragm shortening is also a function of the level of the diaphragm’s workload. For example, when contracting against a very stiff lung or chest cage, the degree of shortening for a given activation and contractility will be far less than when the respiratory workload is normal. For some uses, these complicating effects do not matter. Diaphragm shortening will increase when the respiratory workload is low, when

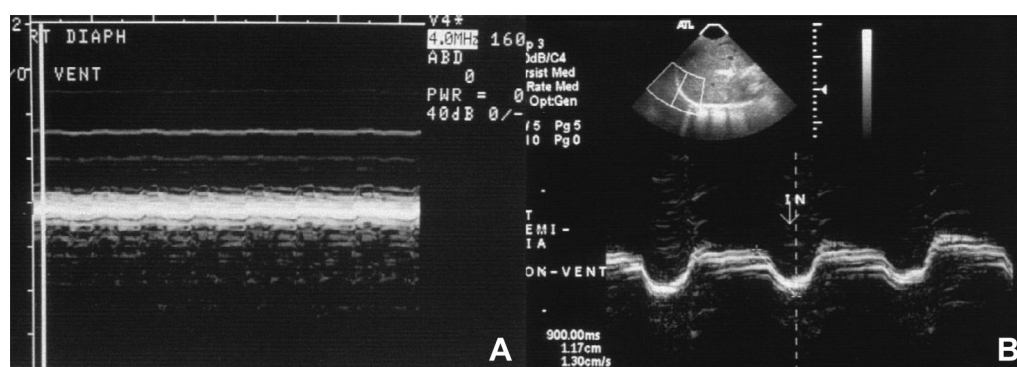


Figure 4 – Diaphragm paralysis. A, Paralysis in the right hemidiaphragm of a 15-year-old boy. As indicated, the M-mode tracing shows no diaphragmatic motion. B, M-mode tracing in another patient with right hemidiaphragm paralysis. Note that there is paradoxical (upward) diaphragm motion during inspiration (arrow). (Reprinted with permission from Gerscovich et al⁵⁶).

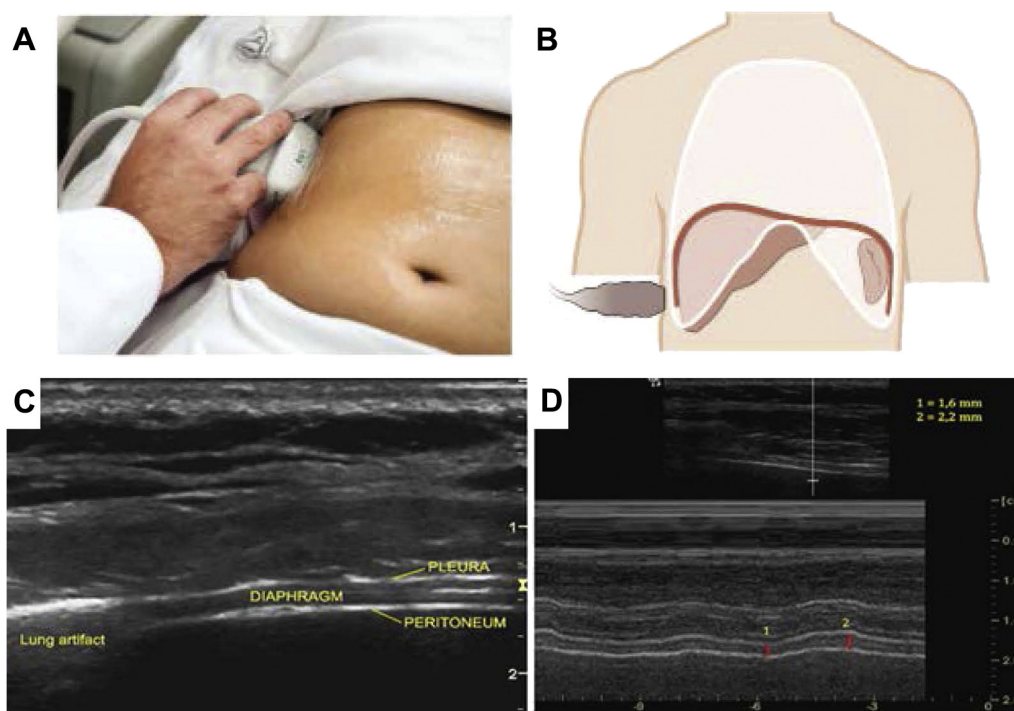


Figure 5 – Diaphragm thickening. A, Probe position for B- and M-mode diaphragmatic thickness measurements in the zone of apposition using a 6- to 13-MHz probe. B, Position of transducer at the zone of apposition and the path of the ultrasound beam. C, B-mode ultrasonography of the diaphragm in the zone of apposition, the diaphragm is visualized as a three-layered structure composed of two parallel echogenic layers of diaphragmatic pleura and peritoneal membranes sandwiching a nonechogenic layer of diaphragm muscle. Lung artifact is seen on the left side of the image. D, M-mode tracing, where 1 is the thickness at end expiration (1.6 mm) and 2 is the thickness at end inspiration (2.2 mm). (Adapted with permission from Sarwal et al⁵⁵ and Zamboni et al⁵⁷).

respiratory drive is adequate and not limited by sedation, and when the diaphragm is strong; all these factors should facilitate weaning from mechanical ventilation, and greater diaphragm shortening should therefore be an excellent predictor for weaning from mechanical ventilation, as recently shown.⁶⁷ Conversely, poor diaphragm shortening can easily be due to inadequate drive or a high respiratory workload and, taken in isolation, cannot be viewed as a direct index of diaphragm strength.

Despite these challenges, current ultrasonographic investigations of diaphragm function in mechanically ventilated patients have provided significant insights into the complexities that alter the diaphragm during mechanical ventilation. However, existing studies on the use of diaphragm ultrasonography are primarily observational, and to date there are no randomized controlled trials published on the use of diaphragm ultrasonography in critical care.⁵⁷ Although this tool has been used to detect diaphragm dysfunction, predict extubation success, and assess atrophy during mechanical ventilation, future randomized controlled trials will be needed to determine if the use of diaphragm

ultrasonography impacts acute and long-term outcomes in critical illness.⁵⁷

Other Techniques to Diagnosis Diaphragm Dysfunction in Mechanically Ventilated Patients

In addition to diaphragm ultrasonography, there are a number of other techniques that are useful in assessing respiratory muscle and diaphragm function in patients in the ICU. A traditional measurement is the maximum inspiratory pressure (also referred to as negative inspiratory force). This measurement can be made with relatively simple equipment and involves attaching a pressure transducer to the inspiratory limb of a two-way valve connected to the patient's airway. The inspiratory limb is then occluded and, with encouragement, the patient is asked to make a series of maximal inspiratory efforts. The major limitation to this assessment is ensuring that the inspiratory effort is truly maximal. When assessed in sedated or uncooperative patients or when there is poor technique, this measurement can be extremely unreliable, as documented in several previous reports.^{12,15,46,68} However, when carefully performed,

this index can be a good predictor of weaning success and other patient outcomes.²⁴

Diaphragm fluoroscopy is frequently used to assess diaphragm movement.¹² When the other respiratory muscles are normal, the patient is cooperative, and unilateral diaphragm paralysis is present, this test can usually provide confirmation of the presence of unilateral paralysis. In this condition, the paralyzed muscle rises with a sharp inspiration while the contralateral diaphragm descends, albeit both false-positive and false-negative results have been reported. This test is unreliable, however, if global weakness is present or if the patient does not cooperate. Fluoroscopy is also unreliable for the diagnosis of bilateral diaphragm paralysis.

Arguably, the gold standard for assessing diaphragm strength is determination of transdiaphragmatic pressure generation in response to controlled exogenous activation of the phrenic nerves bilaterally with either electrical or magnetic stimulation.^{69,70} When this approach is used, the airways are transiently occluded prior to stimulation to limit diaphragm shortening, and phrenic stimulation is applied at the end of expiration, when diaphragm length is at its maximum during the breathing cycle. In addition, the level of current or magnetic field strength applied to the phrenic nerves is adjusted to supramaximal levels to ensure maximal activation of all motor fibers in the phrenic nerve. Although the phrenic nerves can be stimulated with either magnetic or electrical stimuli and over a range of stimulation train frequencies, use of electrical stimulation or high stimulation frequencies increases the discomfort associated with the measurement. As a result, this technique is performed using magnetic stimuli and with single impulses, that is, twitches, to minimize discomfort. Classically, this test is performed after transnasal insertion of small balloon-tipped catheters into the stomach and esophagus. Transdiaphragmatic pressure is then determined by electronically subtracting the esophageal pressure from the gastric pressure. Recently, a number of investigators have modified this technique by eliminating the insertion of the esophageal and gastric balloon-tipped catheters and measuring airway pressures at the mouth in response to BAMPs.^{7,9,10} Unfortunately, these techniques are complex and available in only a few highly specialized centers.

Another test, if available, is the measurement of phrenic nerve conduction times,^{12,71} which can be used for diagnosing unilateral and bilateral diaphragm paralysis. For example, complete absence of phrenic nerve

conduction plus lack of diaphragm movement on ultrasonography would support a diagnosis of diaphragm paralysis due to phrenic nerve damage/pathologic condition. There are, however, important technical issues that may limit interpretation of findings from this test.¹² As a result, this latter test is technically challenging and should be performed only by experienced laboratories.

Treatment of Diaphragm Dysfunction

In all patients with muscle weakness, easily diagnosed and treatable disorders should first be evaluated. Specifically, initial testing should include the assessment and treatment of electrolyte abnormalities and hypothyroidism. Second, there should be consideration that some patients with muscle weakness may have systemic myopathic disorders. These disorders should be especially suspected if mechanically ventilated patients present with significant diaphragm weakness and otherwise unexplained respiratory failure (ie, with clear chest radiographs and normal lung mechanics). It should be remembered that several muscle diseases (myasthenia gravis, adult-onset Pompe disease, chronic inflammatory demyelinating polyneuropathy, and carnitine deficiency) are treatable and can present with primary respiratory muscle involvement and acute respiratory failure.

However, as explained earlier, the most common causes of respiratory muscle weakness in the ICU are systemic inflammatory processes, for example, infections and ventilator-induced diaphragm inactivity. Since infections are a major risk factor for the development of diaphragm weakness, measures to adequately and expeditiously treat infections are clearly an important basic strategy to minimize diaphragm weakness in patients in the ICU. A second approach to the treatment of infection-induced diaphragm dysfunction is the use of pharmacologic agents targeted to improve muscle strength and endurance. One group of agents that are potential candidates for this purpose are drugs that inhibit deleterious pathways (such as proteolytic pathways) previously identified in animal models of infection as causes of diaphragm weakness.^{50,72-74} A second group of agents that could potentially prove efficacious are drugs that alter upstream signaling pathways that improve muscle protein synthesis (eg, mammalian target of rapamycin activators and anti-myostatin-receptor antibodies).^{73,75} Both groups of agents are currently being tested in preclinical trials.

VIDD is also a potentially treatable form of ICU-acquired diaphragm dysfunction. Mechanically ventilated critically ill patients in the ICU are often heavily sedated and ventilated with modes of mechanical ventilation that minimize respiratory motor drive and are sometimes paralyzed for prolonged periods with neuromuscular blocking agents. All these interventions minimize respiratory motor drive, predisposing to VIDD. Often, simple measures can minimize these risk factors.

Currently, sedative regimens are frequently titrated based on behavioral and cognitive indices, but it seems reasonable that such regimens should also take into account respiratory drive to ensure that sedation is not so intense as to ablate breathing efforts. Ventilator settings should also be adjusted to ensure, whenever possible, that patients are making breathing efforts (eg, by assessing patient-ventilator triggering and P_{100} indices of drive). Such bedside strategies should theoretically abolish diaphragm inactivity and minimize VIDD.

However, it has never been shown that it is possible to completely prevent or reverse diaphragm weakness in mechanically ventilated patients by minimizing the effects of infection and VIDD. One potential treatment that may be useful as an additional form of therapy would be to add muscle-specific forms of exercise. Such therapies include various forms of volitional or electrically induced exercise directed at various limb and respiratory muscles. In particular, inspiratory muscle training has been shown to significantly improve diaphragm function.⁷⁶⁻⁷⁸ More recently, catheter-based transvenous phrenic pacing has been suggested as a potential modality to treat ICU-acquired diaphragm dysfunction,^{79,80} albeit studies of this latter form of treatment are just beginning. Although it is also possible that whole body exercise (eg, walking in mechanically ventilated patients) may also improve diaphragm strength or endurance, we are not aware of a study that has directly shown such an effect.

Finally, there are a few special conditions that warrant consideration of specific complex therapies. Intercostal nerve-to-phrenic nerve grafts have been successfully performed to restore diaphragm function in patients with unilateral paralysis.⁸¹ In addition, another treatment for unilateral paralysis is to perform plication of the diaphragm in patients with significant symptoms that fail to resolve during sustained observation.^{82,83} In patients with high-level spinal cord injuries and intact phrenic nerves, diaphragm pacing is an accepted modality of treatment, as recently reviewed by Le Pimpec-Barthes et al.⁸⁴ Ventilator weaning rates of

72% to 96% have been reported with these techniques in patients with high-level spinal cord injury, with no surgery-associated mortalities and with an improvement in quality of life.⁸⁴ Conversely, phrenic nerve pacing is of unproven benefit in treating patients with diaphragm weakness due to systemic neuromuscular diseases and has been shown to increase mortality when used to treat patients with amyotrophic lateral sclerosis.⁸⁴

Conclusions

Diaphragm dysfunction is a common medical problem and can occur in response to a range of underlying medical disorders, with consequences that can be relatively mild to life-threatening. In particular, recent work indicates that diaphragm weakness occurs frequently in mechanically ventilated patients and has significant acute and chronic adverse consequences for these patients. A number of techniques are available to evaluate diaphragm dysfunction. The best method to diagnose a specific patient depends on the specific form of diaphragm dysfunction being investigated and the local availability of advanced techniques. Treatments are also disease specific and can range from serial assessment over time to more innovative approaches such as diaphragm pacing.

Increased clinical awareness of the effects of critical illness on respiratory muscles and the consequences of diaphragm dysfunction in mechanically ventilated patients, as well as implementation of strategies to avert this form of organ failure in critical illness, may improve outcomes in these patients. Nevertheless, future studies are needed to identify additional therapies to prevent diaphragm weakness and improve respiratory muscle endurance in patients with critical illness.

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