Progress in Research on Mechanical Ventilation and Diaphragm Dysfunction

Dilida Duziyelebai [1], Yugang Zhuang [2, *]

[1] Department of Emergency Medicine, Shanghai Tenth People's Hospital, Shanghai 200072, Shanghai, China

[2] Department of Critical Care Medicine, Shanghai Tenth People's Hospital, Shanghai 200072, Shanghai, China

Abstract. Mechanical ventilation is clinically used to assist in the gas exchange for patients who need to maintain adequate alveolar ventilation. Its common indications include respiratory failure, heart failure, drug overdose, and surgery. Although mechanical ventilation can save the lives of patients with respiratory failure, prolonged use can lead to diaphragm atrophy and contraction dysfunction. Currently, there is a lack of effective assessment and monitoring methods for diaphragm dysfunction in clinical practice, leading to insufficient attention to diaphragm function. Understanding the pathophysiological process of diaphragm dysfunction, assessment methods, and prevention and treatment strategies is crucial for improving the prognosis of ICU patients on mechanical ventilation. This paper briefly introduces the pathogenesis of diaphragm dysfunction, current assessment methods, and prevention and treatment strategies, hoping to provide some assistance to clinical practice.

Keywords: Mechanical ventilation, Diaphragm dysfunction, Diaphragm function assessment, Diaphragm-protective ventilation strategies.

1. Anatomy and Physiology of the Diaphragm

The diaphragm is the boundary between the abdominal and thoracic cavities, a dome-shaped thin and broad muscle that bulges upwards, facing the thoracic cavity, and downwards towards the abdominal cavity. The diaphragm is the primary inspiratory muscle, responsible for 60-80% of the work during ventilation.

When the diaphragm contracts, the dome of the diaphragm descends, increasing the volume of the thoracic cavity, aiding in inspiration; when the diaphragm relaxes, the dome of the diaphragm rises, decreasing the volume of the thoracic cavity, aiding in expiration. Another key factor affecting the effectiveness of diaphragm contraction is lung capacity. As lung capacity increases, the inspiratory action of the diaphragm decreases in force, and the pressure generated by diaphragm contraction almost linearly decreases. This is because the diaphragm fibers lengthen, placing them in an unfavorable position for contraction. This effect of lung capacity exists physiologically throughout the entire normal respiratory cycle [1, 2].

The respiratory function of the diaphragm is not limited to inhalation or exhalation. The diaphragm is involved in a series of activities, including coughing, expectoration, sneezing, and other complex activities.

2. Common Causes of Diaphragm Dysfunction

Diaphragm dysfunction can be seen in various situations, such as 1) primary respiratory diseases: studies have found that the inspiratory muscle strength of patients with chronic obstructive pulmonary disease decreases as the severity of the disease increases [3]. 2) Metabolic or inflammatory diseases: for example, the respiratory neuromuscular function of diabetic patients can be affected when the disease progresses to moderate to severe polyneuropathy [4]. 3) Severe neuromuscular diseases/myopathies: patients in the intensive care unit are at high risk for polyneuropathies, and critical illnesses such as polyneuropathies and myopathies in the ICU lead to "ICU-acquired muscle weakness" [5, 6], which also affects the diaphragm, leading to diaphragm dysfunction. 4) Surgical

procedures: surgical procedures such as cardiac surgery has a higher incidence of diaphragm dysfunction, which may be related to direct damage to the diaphragm or phrenic nerve during surgery or the use of cold solutions to cool the heart during surgery [7, 8]. 5) Medications: various medications have a negative impact on respiratory muscle function - such as corticosteroids, sedatives, or muscle relaxants [5, 9, 10]. 6) Mechanical ventilation: mechanical ventilation is a common intervention in the ICU. Although it is a life-saving measure, mechanical ventilation is a cause of many complications. Ventilator-associated lung injury has been confirmed as a common complication of mechanical ventilation, and more and more studies suggest that mechanical ventilation can induce diaphragm dysfunction, also known as ventilator-induced diaphragm dysfunction (VIDD). Diaphragm dysfunction is not only a sign of disease severity, but also a poor prognostic factor for ICU patients [11]. This article will discuss the research progress on the mechanisms of diaphragm dysfunction related to mechanical ventilation and its assessment methods.

3. The Role of Diaphragm in Mechanical Ventilation

3.1. Mechanisms of Diaphragm Injury in Mechanical Ventilation Process

Disuse Atrophy - Excessive Assistive Muscle Injury: Disuse atrophy is the most important physiological mechanism leading to diaphragm dysfunction caused by mechanical ventilation. A classic study showed that brain dead organ donors (with brain death duration of 18-69 hours) exhibited significant diaphragm atrophy [12]. The speed and extent of atrophy are closely related to the degree of respiratory effort suppression [13].

Centripetal Atrophy - Insufficient Auxiliary Muscle Injury: Acute or chronic respiratory overload leading to diaphragm injury, generally occurring on the third day after high-intensity inspiratory load. Muscle biopsies in healthy subjects and patients with chronic obstructive pulmonary disease (COPD) have confirmed the impact of chronic and acute loads on diaphragm injury [14]. Systemic inflammation makes muscle fibers more susceptible to damage, hence critically ill patients are at particularly high risk of load-induced injury [15].

Eccentric Atrophy - Eccentric Muscle Injury: Expiratory contraction causes eccentric load damage [13].When acute lung injury or atelectasis occurs, the diaphragm muscle will maintain continuous contraction during expiration to prevent a decrease in end-expiratory lung volume, a phenomenon known as "exhalation braking" [16] .Due to excessive diaphragm muscle contraction, it eventually leads to diaphragm muscle injury [17].Compared to concentric atrophy, eccentric atrophy causes greater damage [18]. Eccentric atrophy leading to acute diaphragm muscle weakness has been demonstrated experimentally [19].

Longitudinal atrophy - Expiratory muscle injury: Due to the increase in PEEP, the diaphragm muscle fibers maintain a shorter length during the breathing cycle, but when PEEP is rapidly reduced (such as during the weaning period), the diaphragm muscle may be "overstretched" beyond its optimal length and damage diaphragm muscle performance [17].

Therefore, it is crucial to protect the diaphragm and maintain an appropriate level of diaphragm contraction during mechanical ventilation. Monitoring respiratory effort, fine-tuning ventilator settings, and ensuring synchronization between the patient and the ventilator are necessary.

3.2. Diaphragm Function and Ventilation-Perfusion Ratio

For a long time, it has been known that spontaneous breathing can improve ventilation distribution, especially in gravity-dependent regions. The caudal displacement of the diaphragm is greatest during spontaneous breathing and almost eliminated during passive mechanical ventilation. Diaphragm contraction can improve ventilation homogenization. Studies have shown that diaphragm contraction can reduce lung collapse and improve ventilation-perfusion relationships, thereby improving lung respiratory mechanics and oxygenation [20, 21]. As mentioned earlier, mechanical ventilation can cause diaphragm atrophy through various mechanisms, and diaphragm atrophy can progress more rapidly under high assistance [1]. It is conceivable that mechanical ventilation, by causing diaphragm

atrophy and reducing diaphragm contraction strength, can affect ventilation distribution, leading to an imbalance in ventilation-perfusion ratio.

4. Diaphragm Muscle Protective Ventilation Strategy

Just as lung-protective ventilation significantly improves outcomes, diaphragm-protective ventilation represents a new opportunity to accelerate recovery and improve outcomes. With a deeper understanding of the various mechanisms of diaphragm injury, it provides a rational basis for designing new ventilation methods. The primary approach is to maintain an appropriate diaphragm inspiratory effort while avoiding patient-ventilator asynchrony, as patient-ventilator asynchrony may lead to lung and diaphragm injury through increased dynamic lung stress and/or harmful diaphragm contractions [22]. Therefore, diaphragm-protective ventilation strategies require direct monitoring of diaphragm effort and adjustment of ventilation parameters to achieve the effort level.

4.1. Dynamic Monitoring of Diaphragm Function

4.1.1 Electrical Stimulation

1) Electrical Stimulation: There are two feasible methods: electrical stimulation of the phrenic nerve or magnetic stimulation, both based on stimulating the cervical phrenic nerve. Electrical stimulation can cause discomfort, with reports suggesting it may induce seizures; compared to magnetic stimulation, it is more specific for diaphragm stimulation [23, 24]. Magnetic phrenic nerve stimulation causes minimal discomfort, and most patients can tolerate it well. The downside is that magnetic stimulation devices are not easily accessible and expensive.

2) Electromyography: Electromyography is the recording of impulses from the central nervous system, which are converted into action potentials by the phrenic nerve conduction to cause diaphragm muscle contraction. The diaphragm muscle electromyogram detects diaphragm muscle electrical activity (EAdi) through electrodes, and after amplification, filtering, and digital processing, different forms of frequency waves are obtained. There are the following methods for measurement: a. concentric needle electromyography: with each inhalation, regular electrical signals can be seen and characteristic diaphragm muscle motor unit action potentials (MUPs) are recorded. The MUPs of the diaphragm muscle have a short duration and low amplitude, but there are more of them than in chest wall muscles, indicating a lower diaphragm muscle nerve dominance ratio [25]. b. esophageal electrode: esophageal electrodes use a specialized nasogastric tube, located at the junction of the esophagus and the cardia, to record diaphragm muscle electrical activity for continuous monitoring of EAdi, which can obtain better electrical signals and avoid interference from the heart [26]. However, electromyography using esophageal electrodes is invasive and relies on highly specific materials and techniques, making it difficult to obtain.

It is worth mentioning that EAdi reflects respiratory drive output rather than the generation of diaphragm muscle strength. However, there is no consensus on the reference value of EAdi, making it difficult to use this method as a diagnostic indicator for diaphragm dysfunction.

4.1.2 Morphology

Imaging: Currently, diaphragm dysfunction can be evaluated through X-rays, CT scans, or MRI. X-rays have limited specificity, radiation damage, but are relatively inexpensive and can be used as a preliminary assessment tool; CT scans have short examination times, are not affected by respiratory artifacts, and can detect diaphragm and organic lesions through cross-sectional scanning and 3D reconstruction, with higher specificity and sensitivity than conventional chest X-rays, and lower cost than MRI. Therefore, CT has become the main imaging method for studying diaphragm function. However, there are currently no normal standards for quantifying diaphragm indicators; while the advantages of MRI are non-invasive, radiation-free, can directly collect coronal and sagittal images of the entire diaphragm, and can show focal, unilateral, or global diaphragm movement abnormalities. Studies have used MRI to evaluate the diaphragm of long-term mechanically ventilated patients and

found significant focal variations in diaphragm movement in patients with ventilator-induced diaphragm dysfunction [27]. However, MRI requires high operational requirements, is time-consuming, expensive, and both MRI and CT require patients to be transported to the examination room for evaluation, limiting their application in critically ill patients, and making diaphragm function monitoring in mechanically ventilated patients even more difficult.

Ultrasound: In recent years, there has been a significant increase in interest in using ultrasound to assess diaphragm function. With ultrasound, the diaphragm can be explored through two acoustic windows. During diaphragm contraction in inspiration, ultrasound can observe diaphragm inspiratory displacement in the subcostal region, diaphragm thickness at end expiration, and thickening during inspiration [28]. Ultrasound assessment of the right diaphragm is more reproducible and reliable compared to the left, so the right diaphragm is usually chosen [29, 30].

Assessment parameters and methods include 1) Diaphragm displacement: Using a convex low-frequency probe positioned below the right costal margin, between the clavicular midline and anterior axillary line, with the probe marker pointing outward and downward, tracking the posterior third of the right hemidiaphragm in 2D mode. Then, the M-mode detection line is positioned as vertically as possible to the diaphragmatic dome to measure the movement of anatomical structures over time, and then measuring the bottom and top of the diaphragm inspiratory slope to measure diaphragm movement (Figure 1). In critically ill patients receiving mechanical ventilation, the most commonly used criterion for diaphragm dysfunction is diaphragm displacement <10-11 mm [31, 32].

2) Diaphragm Thickness: Select a linear array high-frequency linear probe perpendicular to the lateral chest wall, with the probe marker facing towards the patient's head, positioned between the midaxillary line and the anterior axillary line, between the 9th and 10th intercostal spaces. In 2D mode, identify the pleura and diaphragm, and measure the distance between them as the diaphragm thickness (Tdi); in M mode, place the sampling line perpendicular to the diaphragm, and measure the diaphragm thickness at the end of expiration and the end of inspiration. Diaphragm thickness fraction (TF) is defined as the percentage change in diaphragm thickness during inspiration, i.e. (thickness at end of inspiration - thickness at end of expiration) / thickness at end of expiration (Figure 2). Diaphragm thickness can describe atrophy, while the fraction of thickening represents the inspiratory effort of the diaphragm [28]. In the ICU, mechanical ventilation can rapidly lead to diaphragm injury and thinning [33]. Boon et al. reported a lower limit of normal diaphragm thickness of 1.5mm, with the diaphragm thickness increasing by at least 20% from FRC to total lung capacity [34].

3) Diaphragm Contraction Speed: The diaphragm contraction speed is the ratio of diaphragm displacement to inhalation time. The measurement method is the same as diaphragm displacement, and it is necessary to record the diaphragm displacement and the inhalation time required for the diaphragm to complete the movement. In healthy adults, the diaphragm contraction speed during quiet breathing is approximately (1.3±0.4) cm/s. There is a correlation between the diaphragm contraction speed and the diaphragm muscle strength. Rapid and forceful inhalation helps to accurately assess the strength of diaphragm contraction and can also accurately predict the success rate of weaning off mechanical ventilation in tracheally intubated patients.

Some researchers have proposed that in the future, diaphragm ultrasound new technologies such as tissue Doppler imaging, speckle tracking ultrasound, shear wave elastography, etc., may also be used to evaluate diaphragm function [28]. Compared with other examinations, diaphragm ultrasound has advantages such as no radiation, non-invasiveness, repeatability, fast detection speed, and can be performed at the bedside, reducing the risk of transportation for critically ill patients. However, there are limitations, such as ultrasound imaging depending on the operator's technical level, and sometimes it is difficult to observe the left hemidiaphragm [35, 36].

4.1.3 Diaphragm Strength and Pressure

1) Transdiaphragmatic Pressure: Transdiaphragmatic pressure (Pdi) is the difference between gastric pressure (Pga) and esophageal pressure (Pes). Pdi can be measured using an air-filled latex balloon catheter, a fluid-filled catheter, or a micro-manometer catheter. The method involves placing one catheter in the distal esophagus and one in the stomach, and measuring Pdi during normal

breathing or at maximal inspiration. Because it is a complex and invasive method that requires sophisticated equipment, it is almost exclusively used to assess respiratory muscle strength [37]. Objectively and accurately measuring Pdi is considered the gold standard for diagnosing diaphragm dysfunction [17]. However, it relies on passing catheters through the nose into the distal esophagus and stomach, which may not be easily accessible in most public hospitals, and the correct placement of the catheters depends on experienced examiners; 2) Maximal Inspiratory Pressure (MIP) can also be measured, which is the most widely used method for assessing respiratory muscle strength in patients suspected of respiratory muscle weakness. It is typically performed with the patient sitting, requiring the patient to exhale to residual volume (RV) and then make a maximal inspiratory effort for 1 to 2 seconds. In uncooperative critically ill intubated patients, the optimal measurement of MIP is done using a one-way valve connected to the tube and requires 25 seconds [38]; 3) Pulmonary Function: Once diaphragm dysfunction is suspected, pulmonary function tests are necessary. Vital capacity (VC) from sitting to supine position is a more sensitive and specific method for detecting diaphragm dysfunction, and is the most common screening method for this disorder. The greater the decrease in VC in the supine position, the more indicative of diaphragm paralysis or weakness, with a decrease of 20% or more in △VC in the supine position becoming a reasonable threshold for screening diaphragm dysfunction [39].

4.2. Diaphragm-Protective Ventilation Methods

Diaphragm-protective ventilation is a new concept based on diaphragm injury, and the amount of diaphragm load is directly related to the setting of mechanical ventilation parameters. Excessive support, inadequate support, or patient-ventilator asynchrony can all lead to diaphragm injury. Optimizing ventilator parameters and diaphragm load, reducing patient-ventilator asynchrony, can reduce or avoid diaphragm injury and shorten mechanical ventilation time [17]. The key points of diaphragm-protective ventilation are summarized as follows:

4.2.1. Ventilator Settings

Protective ventilation strategies for the lungs and diaphragm aim to minimize lung pressure and strain while limiting diaphragm atrophy and injury. To achieve these goals, ventilator settings can be adjusted to (1) regulate patient inspiratory effort, (2) minimize dynamic lung pressures, and (3) prevent or correct any form of mismatch between patient-ventilator synchrony or support [22]. Patient-ventilator asynchrony can typically be addressed by adjusting inspiratory trigger settings, current inspiratory time, or cycling criteria.

In some patients, applying higher PEEP may reduce the risk of lung and diaphragm muscle injury: by restoring lung collapse-dependent lung regions to reduce overall and local cyclic lung stress, reduce inspiratory effort [40] and alleviate expiratory braking [41], PEEP can have an important protective effect. However, patients have varying responses to PEEP, requiring careful individualized management.

4.2.2. Proportional Assist Mode

Several studies have shown that NAVA can improve the interaction between patients and ventilators, especially reducing the risk of ineffective efforts and excessive assistance [42, 43]. Proportional ventilation mode amplifies the effort of the patient's respiratory muscle activity, providing necessary support to improve the imbalance between capacity and demand, and simultaneously achieve the patient's ventilation goals. Proportional ventilation mode may prevent lung overexpansion and ventilator over-assistance by maintaining the patient's control mechanism, avoiding diaphragm disuse atrophy, and providing lung and respiratory muscle protective ventilation [43, 44]. NAVA provides proportional inspiratory assistance based on diaphragm electrical activity (EAdi), which closely reflects central respiratory drive and is measured through a dedicated nasogastric tube with embedded electrodes [45]. In one study, NAVA was associated with improved diaphragm function [46]. NAVA improves patient-ventilator interaction, preserves respiratory variability, and allows for better synchronization [47].

Proportional ventilation mode can improve patient-ventilator synchrony, neuro-muscular coupling, and gas exchange, and restore respiratory variability. Proportional ventilation mode can protect patients from the harmful effects of excessive tidal volume, while preventing diaphragm disuse atrophy [47].

4.2.3. Sedation and Analgesia

Sedation can promote protective ventilation of the diaphragm by improving excessive respiratory effort, but complete suppression of respiratory drive and effort may also lead to diaphragm disuse atrophy [42]. Some scholars have found that deep sedation can lead to increased patient-ventilator asynchrony and sedation intensity is positively correlated with mortality [48, 49]. Therefore, appropriate use of sedation methods is crucial, and sedation and analgesia management in mechanically ventilated patients remains challenging.

4.2.4. Auxiliary Therapy

Extracorporeal Carbon Dioxide Removal: Extracorporeal CO2 removal (ECCO2R) is a type of VV-ECMO, with the main function of the membrane lung being to remove excess CO2. ECCO2R reduces the need for ventilation, decreases respiratory effort, and may improve dynamic lung stress. ECCO2R is feasible and effective in reducing tidal volume, driving pressure, and mechanical power in ARDS patients [50]. In spontaneously breathing patients, ECCO2R can suppress respiratory drive and effort [51], contributing to protective ventilation during spontaneous breathing.

Neuromuscular blockade: Complete neuromuscular blockade may increase the risk of diaphragm disuse atrophy and increase sedation requirements. Partial neuromuscular blockade is a compromise between complete paralysis and intense respiratory effort, which can reduce excessive respiratory effort without completely eliminating diaphragm activity [52, 53]. Feasibility studies of partial neuromuscular blockade have been evaluated in concept verification studies of patients with moderate ARDS and high respiratory drive under partial support modes [53].

Phrenic nerve stimulation: Neuromuscular stimulation using electricity to produce muscle contractions without voluntary effort has become an attractive intervention for critically ill patients with loss of ability. Neuromuscular stimulation as a new strategy to maintain or restore respiratory muscle activity, thereby preventing or treating ICU-acquired diaphragm weakness [22]. By inducing diaphragm contractions, neuromuscular stimulation can improve ventilation in dependent lung regions [54]. Reynolds et al. first conducted a series of human temporary phrenic nerve stimulations in surgical patients, demonstrating that this technique can safely and effectively achieve diaphragm muscle contraction [55]. However, there is currently no clinical evidence that ICU patients benefit from phrenic nerve stimulation, and the role in preventing disuse atrophy of the diaphragm is still under investigation.

5. Outlook

Diaphragm dysfunction is common and associated with many adverse outcomes in critically ill patients receiving mechanical ventilation. Diaphragm-protective ventilation is a recent concept aimed at preventing diaphragm injury. Monitoring diaphragm function and identifying diaphragm dysfunction are the basis of these protective strategies. In diaphragm function assessment, transdiaphragmatic pressure induced by phrenic nerve magnetic stimulation is considered the gold standard for objectively assessing diaphragm strength, but it requires the placement of a gastric tube, which affects its clinical application. Ultrasound is superior to methods such as transdiaphragmatic pressure measurement, diaphragm electromyography, and radiological examinations in clinical practice due to its non-invasive nature and real-time bedside observation advantages. Currently, most monitoring tools are invasive and still need improvement, exploration, and development.

In order to implement protective ventilation of the diaphragm, new monitoring, setting of the ventilator, and sedation methods are needed. In the future, auxiliary interventions including extracorporeal life support technology and phrenic nerve stimulation may also play an important role

in specific patients. Due to the complexity of these interventions, assessing the clinical impact of this new model will be challenging.

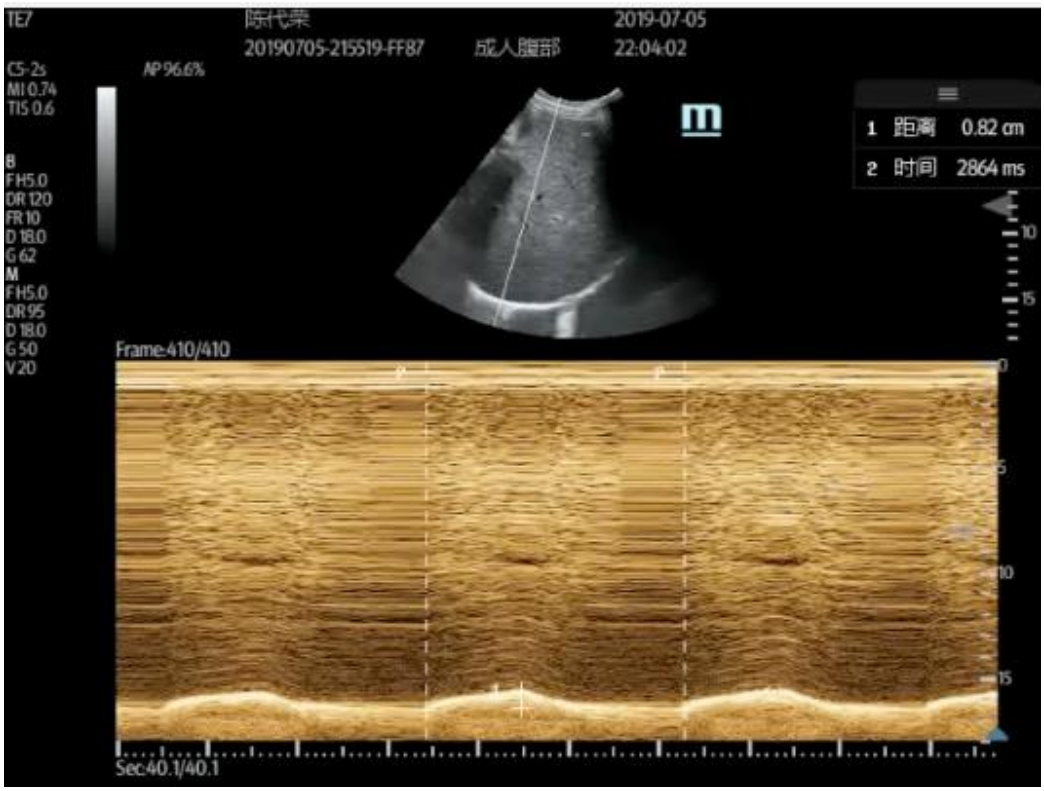

Figure 1. Diaphragm Displacement

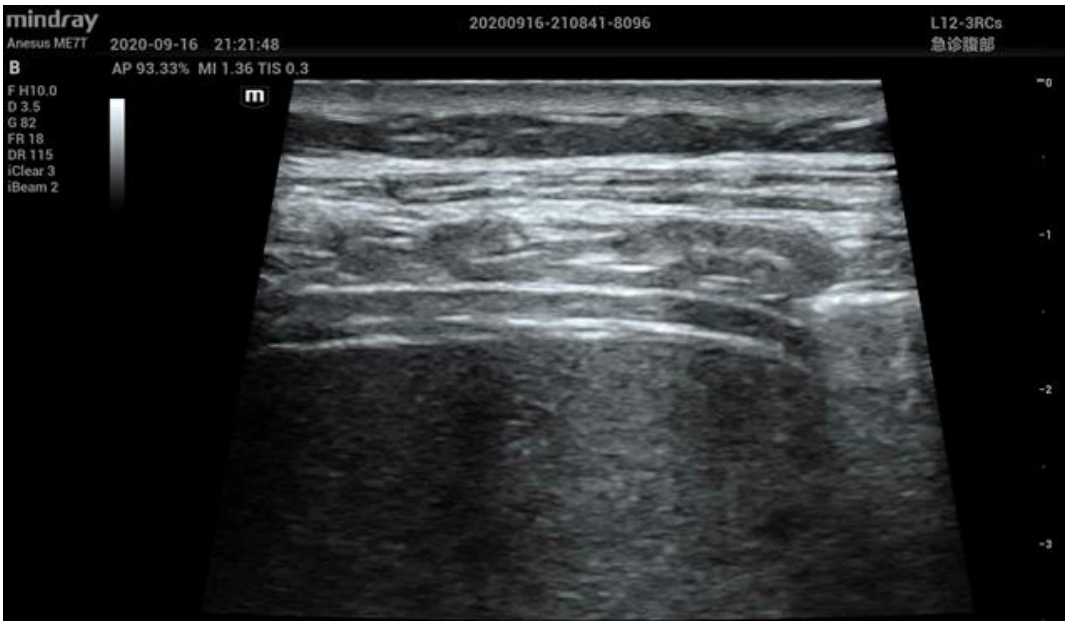

Figure 2. Diaphragm Thickness

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