Diaphragm and Phrenic Nerve Ultrasound in COVID-19 Patients and Beyond

Imaging Technique, Findings, and Clinical Applications

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The diaphragm, the principle muscle of inspiration, is an under-recognized contributor to respiratory disease. Dysfunction of the diaphragm can occur secondary to lung disease, prolonged ventilation, phrenic nerve injury, neuromuscular disease, and central nervous system pathology. In light of the global pandemic of coronavirus disease 2019 (COVID-19), there has been growing interest in the utility of ultrasound for evaluation of respiratory symptoms including lung and diaphragm sonography. Diaphragm ultrasound can be utilized to diagnose diaphragm dysfunction, assess severity of dysfunction, and monitor disease progression. This article reviews diaphragm and phrenic nerve ultrasound and describes clinical applications in the context of COVID-19.

Key Words—COVID-19; diaphragm; phrenic; SARS-CoV-2; ultrasound

Introduction

The global pandemic of coronavirus disease 2019 (COVID-19) has challenged healthcare and scientific communities throughout the world with rapidly evolving medical understanding and practice guidelines. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection primarily affects the respiratory system and can lead to acute respiratory distress syndrome (ARDS) in a subset of patients.1,2 For some patients, respiratory symptoms such as shortness of breath and fatigue persist even after recovery from acute SARS-CoV-2 infection, regardless of the severity of initial SARS-CoV-2 infection.3-5 Diagnostic imaging, including chest radiography and computed tomography (CT), are widely utilized in COVID-19 patients both at the time of initial diagnosis and throughout the disease course.1,6-8 In light of the COVID-19 pandemic, there has been growing interest in the utility of ultrasound to evaluate patients with respiratory symptoms, particularly in regards to lung ultrasound and detection of pneumonia.9 Diaphragm ultrasound, which can diagnose diaphragm weakness, paralysis, and/or phrenic neuropathy as a primary or contributing cause of respiratory symptoms, has also been described in the management of COVID-19 patients, but is not as of yet widely performed.9-11

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Abbreviations
ACE2, angiotensinconverting enzyme 2; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive lung disease; COVID-19, coronavirus disease 2019; CT, computed tomography; EMG, electromyography; POCUS, point of care ultrasound systems; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2

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with expertise in ultrasound imaging have the opportunity to initiate, implement, and/or optimize diaphragm ultrasound protocols. In our experience instituting a diaphragm ultrasound service, we have found that ultrasound is a well-tolerated and informative modality for assessment of the diaphragm and phrenic nerves for both COVID-19 and non-COVID-19 patient alike. In this article, we review diaphragm and phrenic nerve ultrasound and describe clinical applications in the context of COVID-19.

Anatomy and Physiology

The diaphragm is a dome-shaped muscle with a central tendon slip that creates a physical separation between the thorax and the abdominal cavity (Figure 1). Several openings within the diaphragm permit passage of key structures including the great vessels, esophagus, and thoracic duct. Multiple body wall attachments of the diaphragm are present. The xiphoid process, inferior sternum, and the lower 6 ribs and costal cartilage represent anterior and lateral diaphragm attachments. The region of the diaphragm adjacent to the lower rib cage is termed “zone of apposition.” Posteriorly, there are 2 diaphragmatic crura which merge with a fibrous median arcuate ligament and attach to the upper lumbar vertebral bodies and discs. Paired lateral and medial arcuate ligaments contribute to the posterior diaphragm body wall attachment.12–13

The diaphragm is innervated by the bilateral phrenic nerves which provide both motor and sensory function. The phrenic nerves originate from C3 to C5, course through the posterolateral neck, enter the thorax anteriorly, and travel along the anterior pericardium to ultimately reach the diaphragm. At the level of the diaphragm, both phrenic nerves branch into multiple components to innervate the anterolateral, posteromedial, sternal, and crural regions of the diaphragm. Phrenic nerve branches extend along the superior and inferior surfaces of the diaphragm and within the diaphragm muscle itself. In some patients, a smaller accessory phrenic nerve has been described.12–13

The motor component of the phrenic nerve allows

Figure 1. Illustration of diaphragm and phrenic nerve anatomy. Original artwork by David C Botos.
diaphragm muscle contraction. The sensory component involves the diaphragm, pleura, mediastinum, and upper abdomen.\textsuperscript{13}

The diaphragm contracts on inspiration along with accessory muscles of respiration such as the external intercostal, sternocleidomastoid, and scalene muscles. Contraction of the diaphragm results in an increase of diaphragm muscle thickness, caudal movement of the diaphragm, and expansion of the thoracic cavity. As a result, intra-thoracic pressure decreases and intra-abdominal pressure increases allowing for entry of air into the lungs. When the diaphragm relaxes, exhalation results from elastic recoil of the lungs.\textsuperscript{12–13} Given its critical role in respiration, the diaphragm is continuously contracting and highly resistant to fatigue. Both volitional and automatic control of respiration exist, with an intrinsic “diaphragm pacemaker” set by the respiratory control center of the brainstem.\textsuperscript{13}

### Diaphragm Dysfunction

The diaphragm, the principle muscle of inspiration, is an under-recognized contributor to respiratory disease. Dysfunction of the diaphragm (including weakness and paralysis) can occur secondary to a multitude of etiologies including lung disease, prolonged ventilation, phrenic nerve injury, neuromuscular disease, and central nervous system pathology.\textsuperscript{12–13} Theoretical mechanisms of diaphragm dysfunction in COVID-19 patients include critical illness myopathy, ventilator-induced diaphragm dysfunction, iatrogenic phrenic nerve injury particularly secondary to line placement, post-infectious inflammatory neuropathy of the phrenic nerve, or possibly direct neuromuscular involvement of the SARS-CoV-2 virus given expression of the angiotensin-converting enzyme 2 (ACE2) receptor (to which the SARS-CoV-2 viral structural spike (S) protein binds) in the peripheral nervous system and skeletal muscle.\textsuperscript{9,13–19} Interestingly, a recent autopsy study found ACE2 expression in the human diaphragm and SARS-CoV-2 viral RNA in a subset of COVID-19 patients, with increased fibrosis of the diaphragm muscle and a unique myopathic phenotype compared to control-ICU patients.\textsuperscript{20} Further research is needed to elucidate similarities and potential differences in diaphragm dysfunction between COVID-19 and non-COVID-19 patients.

### Table 1. Diaphragm ultrasound protocol at our institution\textsuperscript{a}

| Structure\textsuperscript{b} | Image Acquisition | Patient PROMPT\textsuperscript{c} | Probe | Location\textsuperscript{d} |
|-----------------------------|-------------------|----------------------------------|-------|--------------------------|
| Hemidiaphragm               | Static            | End expiration                   | Linear 14 MHz | Intercostal             |
| Hemidiaphragm               | Static            | Max inspiration                  | Linear 14 MHz | Intercostal             |
| Hemidiaphragm               | Cine clip         | Neutral breathing                | Linear 14 MHz | Intercostal             |
| Hemidiaphragm               | Cine clip         | Neutral breathing                | Curved 8 MHz | Subcostal               |
| Hemidiaphragm               | M-Mode            | Neutral breathing                | Curved 8 MHz | Subcostal               |

**Optional Additional Imaging**

| Structure\textsuperscript{b} | Image Acquisition | Patient PROMPT\textsuperscript{c} | Probe | Location\textsuperscript{d} |
|-----------------------------|-------------------|----------------------------------|-------|--------------------------|
| Phrenic nerve               | Transverse and longitudinal | None | Linear 24 or 18 MHz | Neck, near brachial plexus nerve roots |
| Liver                       | Measurement to assess for hepatomegaly if elevated right hemidiaphragm | None | Curved 8 MHz | Subcostal               |
| Diaphragm                   | Elastography      | None | Linear 14 MHz | Intercostal             |

\textsuperscript{a}Chest radiography and CT are utilized at our institution for imaging evaluation of the lungs; therefore, we do not include lung ultrasound in our protocol. Based on institutional practices, incorporating lung ultrasound into the diaphragm protocol may be considered as indicated.

\textsuperscript{b}Bilateral imaging should be obtained.

\textsuperscript{c}Patient prompts include max inspiration and end expiration (ie, “take a deep breath, hold, let it all out”) and imaging during neutral or normal breathing. If abnormal diaphragm contractility and/or excursion is detected, the patient can then be prompted to breathe deeply while additional images are obtained.

\textsuperscript{d}Location. Intercostal: Position probe between anterior-axillary and mid-axillary lines at the level of the lower rib cage, perpendicular to the chest wall with probe spanning 2 ribs (typically between 9th and 10th intercostal space). Subcostal: Utilize liver window on right and spleen window on center for visualization of the diaphragm.
For patients with both acute and chronic respiratory symptoms, evaluation of the diaphragm may be indicated for diagnosis of diaphragm dysfunction and to guide clinical management strategies. Electrodiagnostic studies such as phrenic nerve conduction studies and diaphragm electromyography (EMG) may be considered, but these studies are invasive, technically challenging, limited by both false positive and false negative results, carry risk of pneumothorax, and may not be readily available at all institutions/hospitals.\textsuperscript{21} Pulmonary function tests offer only indirect measurement of diaphragm function and techniques such as trans-diaphragmatic pressure measurement are invasive, not readily available, and may cause patient discomfort.\textsuperscript{22} Radiography and CT can suggest the possibility of unilateral diaphragm paralysis in the case of hemidiaphragm elevation, which is neither sensitive nor specific for diaphragm dysfunction.\textsuperscript{13,22} While the fluoroscopy sniff test can assesses diaphragm excursion and potentially diagnose paradoxical movement, it has poor sensitivity and is not portable (as may be desired for COVID-19 patients).\textsuperscript{21,23} In contrast, ultrasound is portable, noninvasive, and has both high sensitivity and specificity for detection of diaphragm dysfunction.\textsuperscript{21,23} Furthermore, ultrasound provides comprehensive information on the diaphragm including muscle size, contractility, and excursion.\textsuperscript{21,23} With recent advancements in sonographic technology, high resolution ultrasound can also evaluate the phrenic nerves in the neck.\textsuperscript{24}

**Diaphragm Ultrasound Technique**

Our diaphragm ultrasound protocol is summarized in Table 1. Sonographic examination of the bilateral hemidiaphragms includes measurement of muscle size to evaluate for potential atrophy, analysis of muscle contraction and thickening ratios at maximum inspiration and end expiration, and assessment of diaphragm excursion with M-mode imaging. Pertinent findings such as the presence of pleural effusions or hepatomegaly should be reported. The phrenic nerve is identified...
at the level of the upper brachial plexus nerve roots and can be assessed for size and echogenicity.

The hemidiaphragms are visualized sonographically with intercostal and subcostal approaches (Figure 2). The intercostal approach, with a linear high frequency probe positioned perpendicular to the chest wall between the anterior-axillary and mid-axillary lines typically at the 9th–10th intercostal space, allows for assessment of the zone of apposition where diaphragm thickness and contractility during respiration are measured. The hemidiaphragm is readily identified as a hypoechoic muscle with a hyperechoic central tendon slip, located between the hyperechoic pleural and peritoneal lines, deep to the intercostal muscles (Figure 3A–C). The subcostal approach, with a curved lower frequency transducer positioned in the anterior subcostal region between the anterior axillary and mid clavicular lines, allows for assessment of diaphragm excursion utilizing the liver window on the right and the spleen window on the left. The hemidiaphragm is visualized as an

Figure 3. Normal diaphragm and phrenic nerve ultrasound in a healthy volunteer. A, Illustration depicts diaphragm anatomy as seen on ultrasound with an intercostal window. B, Ultrasound of the right hemidiaphragm utilizing an intercostal window at expiration demonstrates normal muscle size with no evidence of atrophy (thickness >0.15). The diaphragm (calipers) is identified as the muscle between the hyperechoic pleural and peritoneal lines, with a characteristic central tendon slip. C, Ultrasound of the right hemidiaphragm utilizing an intercostal window at inspiration demonstrates intact contractility function with appropriate increase in size of the muscle compared to the expiration image (thickening ratio > 1.2). D, Ultrasound of the right hemidiaphragm utilizing a subcostal window is performed to assess excursion. Cine clips during breathing can demonstrate intact versus decreased motility of the hemidiaphragm. Direct observation by the radiologist is helpful for determining paradoxical movement. Any pertinent findings such as pleural effusion or hepatomegaly should be noted in this view. E, M-mode ultrasound of the right hemidiaphragm utilizing a subcostal window demonstrates normal excursion. F, Sheer wave elastography of the hemidiaphragm can be performed utilizing the intercostal probe position, by placing the region of interest (pink oval) within the diaphragm muscle. G, H, Longitudinal and transverse ultrasound of the right phrenic nerve (calipers) in the neck demonstrates normal size and echogenicity of the nerve. I, Color Doppler ultrasound may be useful for differentiating the phrenic nerve from adjacent vessels.
echogenic line separating the thorax from the abdomen (Figure 3D). M mode imaging allows for measurement of excursion during respiration (Figure 3E).\textsuperscript{10,22}

Shear-wave elastography of the diaphragm has been described in both healthy and critically ill patients, as a method of measuring muscle quality (Figure 3F).\textsuperscript{25} While not widely utilized clinically at this time, diaphragm elastography is certainly promising. Shear-wave elastography may be of particular interest in COVID-19 patients considering a recent autopsy study reporting increased fibrosis of the diaphragm muscle; however, it has yet to be established as a validated diagnostic tool.\textsuperscript{20} Further research is needed regarding clinical applications and normative values for diaphragm elastography.

An ultrahigh resolution linear probe (18–24 MHz) is recommended for evaluation of the bilateral phrenic nerves which travel along the superficial surface of the anterior scalene muscle (Figure 3G–I). The origin of the phrenic nerve from the C3–C5 nerve roots is usually not readily identifiable on ultrasound due to the deep location. The transverse cervical artery may serve as a useful landmark for identification of the phrenic nerve, although Doppler imaging is suggested to avoid accidentally mistaking the artery for the nerve.\textsuperscript{24}

Diaphragm ultrasound scanning technique is best practiced on healthy volunteers who are able to follow breathing commands and can tolerate scanning of the neck. Virtual training sessions may also be helpful to those new to the technique.

### Imaging Findings

Diaphragm ultrasound can assess for muscle size, thickening with respiration, and excursion. Normative values for all 3 measurements have been reported in the literature (Table 2).\textsuperscript{10,22,26–28} Given variability of and relatively limited information on quantitative diaphragm ultrasound metrics in different patient populations, however, additional qualitative assessment of contraction and excursion by a radiologist is valuable.

Diaphragm size is assessed by measuring muscle thickness at end expiration in the zone of apposition, with less than 0.15 cm considered abnormal.\textsuperscript{22} There may be side-to-side differences in hemidiaphragm thickness, up to 0.33 cm.\textsuperscript{22} Assessment of diaphragm muscle size is particularly helpful with serial diaphragm ultrasound exams, to monitor an individual patient’s disease progression versus recovery.

**Figure 4.** 59-year-old female with prolonged hospital course for COVID-19 involving intubation and prone positioning. Her hospital course was complicated by tracheal stenosis status post tracheal resection and anastomosis with multiple subsequent episodes of acute mixed respiratory failure requiring multiple reintubations. Clinical concern was for left hemidiaphragm dysfunction as a contributing factor to her on-going post-COVID-19 respiratory symptoms. **A**, Ultrasound of the left hemidiaphragm (calipers) on expiration demonstrates normal muscle size (thickness >0.15 cm). **B**, Ultrasound of the left hemidiaphragm (calipers) on inspiration demonstrates minimal increase in size of the muscle, compatible with poor contractility function (thickening ratio <1.2).

#### Table 2. Normative Values for Diaphragm Ultrasound\textsuperscript{a}

| Measurement                              | Lower Limit of Normal |
|-----------------------------------------|------------------------|
| Hemidiaphragm thickness                 | 0.15 cm                |
| Hemidiaphragm contractility ratio        | 1.2                    |
| Excursion with quiet breathing          | 0.9 cm                 |
| Excursion with deep breathing           |                        |
| Female: 3.6 cm                          |                        |
| Male: 4.7 cm                            |                        |

\textsuperscript{a}References: 22, 27.
potential effect patient positioning (upright versus supine) can have on thickness values, the thickening ratio may be a more accurate method of diagnosing diaphragm dysfunction (Figure 4). Defined as thickness at maximum inspiration divided by thickness at end expiration, the thickening ratio reflects diaphragm contractility with a lower limit of normal of 1.2.22 The diaphragm thickening fraction, defined as (end-expiration thickness – end-inspiration thickness)/end-expiration thickness, is another commonly reported variable with a thickening fraction of <20% diagnostic of diaphragm dysfunction.10

Both quantitative and qualitative methods for evaluating diaphragm excursion have been described. Lower limit normative values for excursion for women and men respectively are 0.9 and 1.0 cm with quiet breathing, 1.6 and 1.8 cm with voluntary sniffing, and 3.7 and 4.7 cm with deep breathing.27 Healthier younger patients with lower body mass index and waist circumference may display decreased diaphragm excursion.28

Of note, appropriate patient effort is needed for accurate measurement of the thickening ratio and thickening fraction.22 Similarly, appropriate patient effort is needed for assessment of diaphragm excursion using M mode ultrasound (Figure 5). In our experience, combining quantitative data, based on cut-off values in the literature, with qualitative interpretation of images is ideal for generating a final impression for the study. Consultation and collaboration with clinical counterparts, including pulmonary and critical care, neurology, physical medicine and rehabilitation, and thoracic surgery specialists is helpful when launching a diaphragm ultrasound service.

Standardization of protocol and image acquisition is also necessary for accurate analyses. Diaphragm ultrasound variations between prone and supine positioning have been described, which is an important

Figure 5. 62-year-old male with history of HIV and prolonged hospital course for COVID-19 related ARDS necessitating intubation and prone positioning. He was discharged to an inpatient rehabilitation facility where he was found to have multiple neuropathies confirmed with electromyography and nerve conduction studies. There was clinical concern for phrenic neuropathy potentially contributing to his ongoing post-COVID-19 respiratory symptoms. A, B, Ultrasound of the right hemidiaphragm (calipers) on expiration and inspiration views demonstrates normal muscle size (thickness >0.15 cm) with decreased contractility function (thickening ratio <1.2). C, M-mode ultrasound of the right hemidiaphragm demonstrates decreased excursion with motility elicited only by promoting the patient to breathe deeply. D, The right phrenic nerve (calipers) was normal in size and echogenicity within the neck.
consideration given the common practice of prone positioning of COVID-19 patients to improve oxygenation. In our practice, we perform all imaging with the patient in the supine position. If patient effort is not deemed as appropriate at baseline, imaging of both neutral (i.e., unprompted) respiration as well as prompted deep breathing is obtained. For patients who are unable to follow any commands, such as in the case of mechanical ventilation, limitations of the study are documented in the report. In our experience, assistance from a respiratory therapist and/or members of the clinical team can be helpful during ultrasound of the diaphragm in ventilated patients. Any pertinent findings, such as pleural effusion, lung consolidation, or hepatomegaly, should also be conveyed to the clinical team and can be further assessed with appropriate dedicated imaging.

In addition to diaphragm imaging, radiologists can offer ultrasound of the phrenic nerves to aid in diagnosis of myopathic verses neurogenic pathology or to assess for iatrogenic phrenic nerve injury. High resolution ultrasound can visualize the phrenic nerve within the neck as it courses superficial to the anterior scalene muscle. Peripheral nerves generally demonstrate a classic honeycomb appearance in the transverse axis on ultrasound, with a hyperechoic epineurium surrounding hypoechoic nerve fascicles. While visualization of the expected honeycomb appearance of the phrenic nerve is not always feasible given its small size, abnormal findings such as nerve enlargement and hypoechogenicity may be appreciated (Figure 6). Comparison of the bilateral phrenic nerves is helpful to assess for symmetry and serve as an internal control. One study found a mean phrenic nerve diameter of $0.6 \times 1.0$ mm (range $0.3-0.8 \times 0.6-1.7$ mm) in healthy volunteers. There is limited literature on phrenic nerve sonography, however, with no data regarding sensitivity and specificity of imaging findings. Abnormal sonographic findings of the phrenic nerve and potential clinical utility of phrenic nerve ultrasound in COVID-19 patients has not been described to date; however, literature on imaging of other peripheral nerves highlights the value of identifying nerve pathology prior to end-organ damage (which in the case of the phrenic nerve would translate to prior to detection of diaphragm muscle atrophy and dysfunction). Furthermore, “hourglass-like” constrictions of the phrenic nerve have been previously described as highly suggestive of neuralgic amyotrophy, which can occur secondary to both viral

Figure 6. 72-year-old male with prolonged hospital course for COVID-19 complicated by invasive pulmonary aspergillosis with multiple post-COVID-19 left upper extremity peripheral neuropathies. Clinical concern was for left phrenic neuropathy. Ultrasound of the bilateral hemidiaphragms demonstrated normal muscle size, contractility, and excursion (not shown). A, B, Longitudinal and transverse ultrasound of the left phrenic nerve (calipers) in the neck demonstrates subtle asymmetric thickening and hypoechogenicity. C, D, Normal appearance of the right phrenic nerve (calipers) in the neck on longitudinal and transverse ultrasound is shown for comparison. In the clinical context, findings were affirmative of a left phrenic neuritis diagnosed prior to onset of end-organ damage (i.e., diaphragm muscle atrophy and dysfunction).
infection and vaccination. Further investigation regarding the theoretical possibility of phrenic neuralgic amyotrophy in COVID-19 patients is needed. In addition, an autopsy series of COVID-19 patients detected SARS-CoV-2 viral proteins in the medulla oblongata and cranial nerves IX and X; whether the phrenic nerves can also be infected by SARS-CoV-2 (thereby contributing to rapidly deteriorating respiratory function in acute COVID-19 illness or alternatively causing chronic shortness of breath in COVID-19 “long haulers”) are hypothetical considerations that warrant further study. Overall, ultrasound of the phrenic nerve is of growing interest particularly in the setting of COVID-19.

**Clinical Applications**

Numerous disorders can lead to unilateral or bilateral diaphragm dysfunction, as outlined in Table 3. Diaphragm dysfunction has potential impact on survival and is associated with symptoms such as dyspnea, sleep disturbance, inability to tolerate exercise, and hypersomnia. Diaphragm ultrasound can be utilized to diagnose diaphragm dysfunction, assess severity of dysfunction, and monitor disease progression versus recovery in a longitudinal fashion. Ultrasound of the diaphragm can be performed in both the inpatient setting, such as for ICU or lung transplantation patients, and in the outpatient setting, such as for patients with chronic obstructive lung disease (COPD) or neuromuscular junction disorders.

In the context of the global COVID-19 pandemic, diaphragm ultrasound is particularly valuable given portability, ease of cleaning, and widespread access to imaging technology with point of care ultrasound systems (POCUS). Monitoring of respiratory muscle performance in COVID-19 patients has recently been proposed, to aid with triaging of patients in times of crisis (and potentially limited ICU resources) and guide implementation of respiratory muscle training. Routine ultrasound screening of the diaphragm in patients with severe lung involvement of SARS-CoV-2 has also been suggested as a means of optimizing treatment and interventions. In patients with positive COVID-19 testing, appropriate personal protective equipment and cleaning measures are mandatory. While the potential ability of SARS-CoV-2 to act as a neuromuscular pathogen is as of yet unclear, diaphragm dysfunction can occur in COVID-19 patients secondary to other mechanisms such as over-exertion in the setting of underlying chronic lung or neuromuscular disease exacerbated by the SARS-CoV-2 infection, critical illness myopathy, ventilator-induced diaphragm dysfunction, and phrenic nerve injury. Diaphragm ultrasound applications in COVID-19 patients are readily translatable to non-COVID-19 patients who may have similar mechanisms of injury.

In ICU patients, ultrasound can diagnose diaphragm dysfunction that may be acquired secondary to ARDS, prolonged ventilation, deep sedation, neuromuscular blockage, and/or permissive hypercapnia. Poor outcome factors and increased mortality are

### Table 3. Potential Etiologies of Diaphragm Dysfunction

| Location                  | Disorder                                      |
|---------------------------|-----------------------------------------------|
| Central nervous system    | Multiple sclerosis                            |
|                           | Stroke                                        |
|                           | Arnold-chiari malformation                    |
|                           | Tetraplegia                                   |
|                           | Spinal cord injury                            |
|                           | Syringomyelia                                 |
| Motor neurons             | Amyotrophic lateral sclerosis                 |
|                           | Poliomyelitis                                 |
|                           | Radiation-induced neuropathy                  |
| Peripheral nervous system | Guillain–Barre syndrome and variants          |
| (generalized)             | Neuralgic amyotrophy (Parsonage–Turner syndrome) |
|                           | Critical illness polyneuropathy               |
| Phrenic nerve (isolated)  | Trauma                                        |
|                           | Iatrogenic injury—Surgery (ie, cardiac, neck/cervical, abdominal, lung transplant) |
|                           | Iatrogenic injury—procedure (ie, central vein cannulation, nerve block, AF ablation) |
|                           | Tumor or mass lesion compression              |
|                           | Infectious (Herpes-zoster, Lyme, HIV)         |
|                           | Traction or stretch injury                     |
|                           | Idiopathic                                    |
| Muscle                   | Muscular dystrophies                           |
|                           | Myositis                                       |
|                           | Glucocorticoids                                |
|                           | Critical illness polymyopathy                 |
|                           | Disuse atrophy (ie, mechanical ventilation)   |
| Neuromuscular junction    | Myasthenia gravis                             |
|                           | Lambert–Eaton syndrome                        |
|                           | Botulism                                       |
| Lungs                    | Chronic obstructive pulmonary disease         |
|                           | Asthma                                         |

References: 13, 22, 34.
associated with both critical illness-induced diaphragm weakness and ventilator-induced diaphragm dysfunction. Ventilator-induced diaphragm dysfunction may manifest as early as 24–26 hours after mechanical ventilation. Numerous prior studies have supported the role of diaphragm ultrasound in predicting weaning outcomes, although further research is needed specific to the COVID-19 subpopulation. Identifying the optimal time for extubation is crucial given risks of both prolonged ventilation versus extubation failure. Furthermore, diaphragm ultrasound may help determine need for tracheostomy. In the literature, there are multiple clinical papers analyzing the utility of diaphragm ultrasound in predicting weaning outcomes. A diaphragm excursion value of <10 mm is associated with weaning failure. A diaphragm thickening fraction of ≥30% predicts weaning success. Since diaphragm dysfunction secondary to critical illness or prolonged ventilation is potentially reversible, outpatient monitoring with serial ultrasound exams may be helpful during the recovery process. Serial measurements of diaphragm thickness can be used to demonstrate progressive muscle atrophy (and poor outcome) over time versus rehabilitation success with training. In our clinical experience with COVID-19 patients, diaphragm ultrasound is particularly helpful for patients with difficulty weaning from mechanical ventilation and for patients who were successfully weaned from prolonged ventilation but continue to experience dyspnea or oxygen requirements.

In surgical candidates such as liver transplant or cardiothoracic surgery patients, diaphragm ultrasound can be utilized to establish pre-operative baseline diaphragm thickness and function, assess for potential new-onset or worsening postoperative diaphragm dysfunction, and aid in predicting postoperative weaning.
At our institution, bilateral lung transplantation has successfully been performed for COVID-19 patients with severe illness as a life-saving measure of last resort. In our experience, diaphragm ultrasound may be helpful for both pre-transplant evaluation of a potential lung transplant candidate as well as post-transplant assessment of diaphragm function (Figures 7 and 8). While patients undergoing lung transplantation may have pre-existing diaphragm dysfunction secondary to severe lung disease and/or prolonged ventilation, the surgery itself can also cause diaphragm dysfunction—potentially from iatrogenic injury of the phrenic nerve. Further investigation is needed to create evidence-based...
Phrenic nerve pathology can occur secondary to iatrogenic injury or as a post-infectious inflammatory neuropathy (neuralgic amyotrophy or Parsonage-Turner syndrome). Neuralgic amyotrophy of the phrenic nerve is an often overlooked condition that can occur secondary to a number of conditions including viral infection, vaccination, surgery, and trauma. Iatrogenic phrenic nerve injury can occur secondary to line placement (including extracorporeal membrane oxygenation [ECMO] cannulation) or thoracic surgery.

Diaphragm ultrasound in patients with phrenic nerve injury may demonstrate muscle atrophy and can document progression versus recovery with serial ultrasound exams over time. Since phrenic nerve/diaphragm muscle recovery can take up to 3 years, serial ultrasound measurements of diaphragm thickness may aid clinical decision-making including determining need for surgical intervention such as...
Further research is needed regarding incidence of phrenic nerve pathology in association with COVID-19.

Additional notable causes of diaphragm dysfunction include neuromuscular disorders and chronic lung disease, both of which may be present in COVID-19 patients and potentially contribute to lingering respiratory symptoms (Figure 9). Prior literature has demonstrated diaphragm dysfunction in the setting of chronic obstructive pulmonary disease (COPD) and asthma (hyperinflation) as well as numerous neuromuscular disorders. Diaphragm ultrasound can monitor disease progression and aid pulmonary rehabilitation efforts, enabling serial non-invasive measurements and potentially serving as a prognostic marker of outcomes. Further research is needed to elucidate the role of outpatient diaphragm ultrasound imaging in both COVID-19 and non-COVID-19 patients as well as implications on rehabilitative care and respiratory muscle training.

**Treatment Strategies**

In patients with clinical suspicion of diaphragm paralysis, ultrasound can be utilized to diagnose diaphragm dysfunction. Management strategies for diaphragmatic dysfunction are based on the etiology and severity of dysfunction. Many otherwise healthy patients with unilateral diaphragm paralysis may be asymptomatic and treated conservatively. Patients with co-morbidities and unilateral diaphragm paralysis
may be symptomatic and complain of dyspnea on exertion or in the supine position. Patients with bilateral diaphragm paralysis typically experience more severe respiratory symptoms.\textsuperscript{12–13} In the acute setting (including patients presenting with COVID-19), diagnosis of diaphragm dysfunction by ultrasound may guide respiratory management decisions such as ventilation and need for ICU-level care.\textsuperscript{11,35} In the chronic outpatient setting (including COVID-19 “long haulers”), treatment options for symptomatic diaphragm dysfunction include noninvasive positive-pressure ventilation, diaphragm plication, phrenic nerve repair by microsurgery, and phrenic nerve or diaphragm muscle pacing.\textsuperscript{12–13,34} Of note, the phrenic nerve is relatively slow to regenerate and may take anywhere from 1 to 3 years to recover after injury.\textsuperscript{14} For this reason, some patients may be managed with serial diaphragm ultrasound exams over time to assess for recovery versus progression and guide decisions regarding need for and timing of surgical intervention.\textsuperscript{42,44} In patients with chronic conditions such as neuromuscular disease and COPD, serial diaphragm ultrasound may be utilized to monitor disease progression and evaluate response to non-surgical management such as respiratory rehabilitation and treatments aimed at improving muscle function.\textsuperscript{10} A suggested algorithm for clinical use of diaphragm ultrasound based on the authors’ experience of >60 diaphragm ultrasounds over the last 6 months is provided in Figure 10.

**Conclusion**

In summary, ultrasound is a well-tolerated noninvasive imaging modality that can accurately evaluate diaphragm function and the phrenic nerves in the region of the neck. Clinical applications for ultrasound imaging of the diaphragm include diagnosis of unilateral or bilateral diaphragm paralysis, longitudinal assessment of respiratory patterns in patients with neuromuscular and/or chronic lung diseases, and monitoring of patients in the intensive care unit. The global pandemic of COVID-19 has led to an increased interest in lung ultrasound including diaphragm functional assessment. Further research is needed to elucidate the effects of SARS-CoV-2 on the diaphragm and phrenic nerves. In our institutional experience however, diaphragm ultrasound is a useful and promising tool for evaluation of acute and chronic respiratory symptoms in COVID-19 and non-COVID-19 patients alike. With appropriate protocols and expertise, radiologists can readily provide diaphragm ultrasound imaging services in both the inpatient and outpatient settings.

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