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Case Report

Diaphragmatic thickening fraction as a predictor for intubation in patients with COVID-19

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ABSTRACT

The diaphragm is the primary respiratory muscle, and its dysfunction predisposes patients to respiratory failure. Diaphragm function can be assessed by ultrasound measurement - Diaphragmatic Thickening Fraction (DTF). Respiratory viral infections (including SARS-CoV-2) can cause diaphragm dysfunction. Our case series follows three patients infected with COVID-19 pneumonia. Bedside diaphragmatic ultrasound assessments measuring DTF were trended over patient's hospital course until clinical improvement (i.e., off oxygen) or worsening (i.e., intubation). Our preliminary results suggest a correlation between DTF trends and respiratory status in patients requiring 100% oxygen. Further studies are required to assess DTF and its possible correlation to respiratory failure.

1. . Background

The diaphragm is a musculotendinous structure that separates the abdominal and thoracic cavity. It functions as the primary respiratory muscle, generating transdiaphragmatic pressure to inhale air into the lung [1]. Diaphragm dysfunction predisposes patients to respiratory complications. Common causes of diaphragm dysfunction can include infection, electrolyte abnormalities, central nervous system disturbance (stroke), or spinal cord injury. These can all cause impending respiratory failure [2]. SARS-CoV-2 infection has been shown to cause diaphragm weakness due to systemic inflammation, disruption in blood flow distribution, impairment of contractility protein, direct myofiber injury, and immune-mediated myopathy [3,4].

Respiratory failure from prolonged respiratory effort can result in occult diaphragmatic dysfunction and poor clinical outcome [5]. Thus far, the timing of intubation in SARS-CoV-2 infection has been dependent on the physician's clinical judgments, as the optimal timing of intubation remains unclear [6].

Diaphragmatic ultrasound has been studied as a non-invasive, quick and reproducible technique to assess diaphragmatic function [7,8]. Diaphragmatic thickening fraction (DTF) and diaphragmatic excursion have shown to be good prognostic markers to predict extubation [9–11]. A recent a study by Corradi et al., showed DTF as a potential predictor of respiratory improvement or progression in patients who were on Continuous Positive Airway Pressure (CPAP) ventilation and required intubation [12].

Our case series aimed to determine the utility of diaphragm ultrasound in patients with SARS-CoV-2 to predict respiratory failure in terms of worsening failure or improvement in patients with varying use of oxygen therapy [not on Non-Invasive Positive Pressure Ventilation (NIPPV) or those intubated]. Failure was defined as intubation, and improvement was defined as a decrease in oxygen requirement.

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2. Methods

We performed bedside diaphragmatic ultrasound assessments, specifically DTF, on patients with varying levels of non-invasive oxygen supplementation such as HFNC and/or Non-rebreather mask (NRB) with hypoxic respiratory failure secondary to COVID-19 pneumonia. DTF was trended over their hospital course at scheduled intervals from admission (Day 1), 24 hrs (Day 2), 48 hrs (Day3), Day 7 (if available) and at intervals when any oxygen requirements changed until clinical improvement or worsening (i.e., intubation) resulted.

DTF was measured using a high frequency (13–6 mHz) ultrasound probe at the right hemithorax costophrenic angle at the mid axillary line with the probe marker facing cephalad. We chose the right hemithorax because the liver can be used as an acoustic window to help aid diaphragm measurements. First, using the low frequency probe, the liver and pleural line are identified coming into view with each breath. Then switching to the high frequency ultrasound probe, the junction between the diaphragm layer and the pleural line known as the zone of apposition was visualized. Optimally the zone of apposition should be centered on the screen. The diaphragm was measured from its pleural layer to its peritoneal layer. (Video 1). We measured the diaphragm at the end of inspiration and at the end of expiration to calculate DTF. The calculation is as follows:[(Diaphragmatic Thickness on end Inspiration (DTi) - Diaphragmatic thickness on end Expiration (DTe))/DTe] and expressed as percentage [13].

Supplementary video related to this article can be found at https://doi.org/10.1016/j.rmcr.2022.101743

3. Case description

3.1. Case A

A 58-year-old female without past medical history (PMH), unvaccinated against SARS-CoV-2, initially presented with ten days of upper respiratory tract infection (URI) symptoms including fever, fatigue, myalgia, rhinorrhea, and worsening shortness of breath. She tested positive for SARS-CoV-2 and presented with SpO2 of 17% requiring HFNC at 40 liters-per-minute (LPM) and 100% Fraction of Inspired Oxygen (FiO2) with an additional NRB mask at 15 LPM. Computer-Tomography Angiography with contrast Pulmonary Embolism (CTPE) protocol showed bilateral pulmonary embolism (right greater than left distal branch) with diffuse bilateral infiltrates and mosaic attenuation. She was admitted to the Medical Intensive Care Unit (MICU), started on dexamethasone, remdesivir, and received tocilizumab infusion. Initial DTF was 0.87 on Day 1. Her oxygenation status and work-of-breathing worsened, and on day 2, her DTF was 0.61 [Fig. 1]. The patient was intubated on Day 3 with worsening Acute Respiratory Distress Syndrome (ARDS), requiring rescue therapies such as prone ventilation and inhaled Nitric Oxide (iNO). Unfortunately, the patient's condition continued to worsen, and she ultimately passed on day 19.

3.2. Case B

A 48-year-old male with PMH of hypertension, autism, prediabetes, unvaccinated against SARS-CoV-2 was admitted for hypoxemic respiratory failure after a two-week history of shortness of breath. On arrival to the ER, he had an SpO2 of 86% on room air with tachypnea and significant work of breathing with use of accessory muscles. He was placed on HFNC with 40 LPM and FiO2 100%,

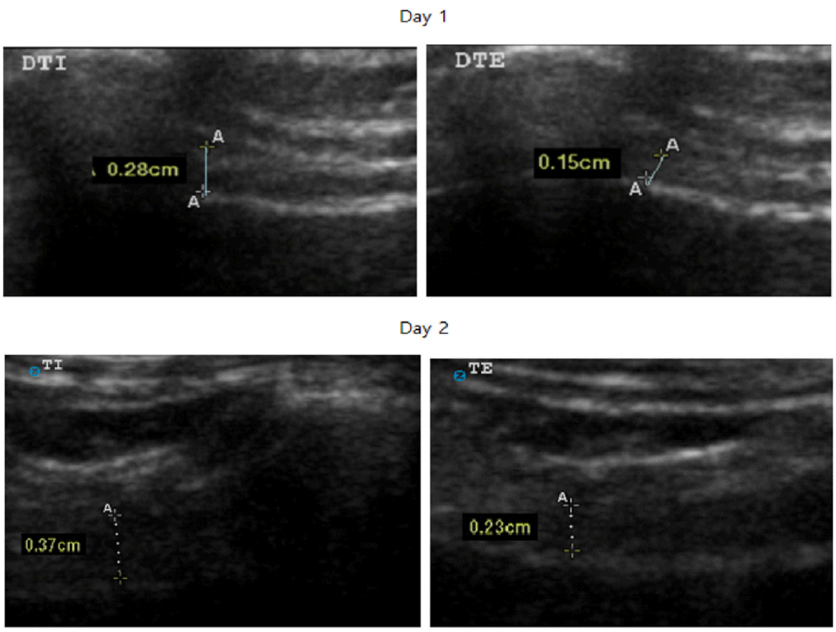

Fig. 1. B mode images of Case A showing DTi 0.28 cm, DTe 0.15 cm with measured DTf of 0.87 cm on Day 1, and DTi 0.37 cm, DTe 0.23 cm with measured DTf 0.61 cm on Day 2: DTi = Diaphragmatic Thickness on end Inspiration, DTe = Diaphragmatic Thickness on end expiration, DTF = Diaphragmatic Thickening Fraction.

Table 1
Measured DTF by sequence during admission: DTF = diaphragmatic thickness fraction.

Case	1st DTF	2nd DTF	3rd DTF	4th DTF	Intubation
A	0.87 cm	0.61 cm			Yes
B	0.83 cm	0.14 cm	0.17 cm		Yes
C	0.27 cm	0.53 cm	0.56 cm	1.2 cm	No

which improved SpO2 to 90%. Chest X-ray (CXR) showed lingular and left lower lobe consolidation with a small left pleural effusion. He was admitted to the general medical floors for hypoxemic respiratory failure due to COVID-19 pneumonia with possible concomitant bacterial pneumonia. The patient was started on ceftriaxone, azithromycin, dexamethasone, remdesivir, and tocilizumab. DTF on admission was 0.83. On Day 2, he was upgraded to MICU due to worsening hypoxemia and work of breathing. DTF decreased to 0.14 [Table 1]. NRB was placed on top of HFNC. On Day 6, he became more tachypneic, and DTF prior to intubation was 0.17. He subsequently developed septic shock, requiring vasopressors. He was started on prone ventilation for the next five days and extubated on Day 14 to HFNC, which was subsequently weaned down to room air and later discharged from the hospital after a long course.

3.3. Case C

A 56-year-old female with no significant PMH, unvaccinated against SARS-CoV-2, presented with a three-day history of watery diarrhea, shortness of breath, and recent travel history to Mexico. She was admitted for hypoxemic respiratory failure secondary to COVID-19 pneumonia, initially requiring 5 L NC with SpO2 93%, which was subsequently increased to NRB. DTF on Day 1 was 0.27. She was treated with remdesivir, dexamethasone, and therapeutic dose of anticoagulation with enoxaparin. On Day 3, DTF increased to 0.53, and she appeared more comfortable though she remained on NRB. On Day 4, DTF was 0.56; supplemental oxygen support was titrated down to 6L NC. At this time, inflammatory markers were also trending down. On Day 5, DTF increased to 1.2, and she was successfully weaned off supplemental oxygen. She was then discharged on Day 7.

4. Discussion

Our current research on this topic and other studies [5,12–14] suggest that there may be a possible association between worsening or improving respiratory failure and DTF. Our three cases perhaps suggest that when the DTF declines, a decline in the patient's respiratory status follows. Alternatively, when DTF improves, the patient's oxygen requirements lessen. However, there are important confounders to mention. Sepsis and critical-illness [15,16] may intrinsically lead to diaphragm dysfunction and, therefore, a lower DTF; as opposed to decreased DTF being the modifying factor for worsening respiratory failure. A limitation to this study is its obvious small sample size; however, given this trend in our pilot case series and previous studies [5,12–14], diaphragm ultrasound, especially in terms of DTF, may be underutilized in respiratory viral infections. During the COVID-19 pandemic, bedside ultrasound was widely utilized as a rapid, non-invasive imaging modality to identify lung involvement [14]. DTF measurements, though not commonly taught, have been found to have good reproducibility [5,17–19].

Recently, questions have been raised about the utility of DTF to prognosticate respiratory status in SARS-CoV-2 populations [12]. Our findings and similar findings by Corradi et al. [12], may suggest an interesting association on DTF possibly having predictive value regarding respiratory failure.

An essential distinction in our study from others is that our population did not receive NIPPV or positive pressure invasive mechanical ventilation when measurements were taken. Positive Pressure ventilation assists the patient's breath and offloads respiratory work [18]. Murine models have shown positive pressure ventilation reduces total and regional diaphragm perfusion [20]. Our patient population were all on HFNC or NRB; therefore, their DTF depended entirely on their own effort.

The recent COVID-19 surges have changed the way clinicians may choose to intervene in respiratory failure especially in terms of intubation. The current COVID-19 pandemic led to overwhelming the health system with initial uncharted data and dwindling resources. This strain led clinicians to make decisions based on general non-specific inflammatory markers (based on their prognostic value [21]) or illness severity scores, in addition to traditional objective data (i.e., respiratory rate, oxygenation trends).

More so, given limitations in the allocation of ventilators, a decision on whether to intubate or not became critical. A meta-analysis by Papoutsi et al. [6], showed no statistically detectable difference on all-cause mortality between patients undergoing early versus late intubation. Given this lack of clear guidance on optimal time to intubate, a real time functional assessment of the largest respiratory marker/muscle-the diaphragm and DTF, warrants further research efforts especially in terms of trends and cut off values. Trending DTF may provide supplemental information/data in patients with respiratory failure to further assist in their management.

Declaration of competing interest

None.

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