

Case report

Thickening fraction as a measure of ultrasonographic diaphragm dysfunction in amyotrophic lateral sclerosis



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ARTICLE INFO

Article history:

Received 30 September 2019
 Received in revised form 17 January 2020
 Accepted 21 January 2020
 Available online 30 January 2020

Keywords:

Motor-neuron disease
 Neuromuscular disease
 Thickening fraction of diaphragm
 Diaphragm dysfunction
 Diaphragm thickness
 Ultrasonography

ABSTRACT

Objective: Respiratory failure is the most common cause of death in ALS patients secondary to diaphragmatic dysfunction. Herein, we report three ALS patients, and we sought to determine the diaphragm dysfunction by the measurement of ultrasonographic diaphragmatic thickness fraction (DTf).

Methods: High-resolution linear US probe of 10 MHz (Philips Healthcare EPIQ 7 Ultrasound System Inc.) was used to measure the diaphragm thickness (DT) using B mode at the Zone of Apposition. Phrenic nerve compound muscle action potential measured stimulating the nerve, posterior to the sternocleidomastoid muscle, approximately 3 cm above the clavicle and recording the diaphragm with electrode G1 placed fingerbreadth above the xiphoid process and electrode G2 placed over the anterior costal margin 16 cm from G1.

Results: The diaphragmatic thickening fraction (DTf) measured in these three patients recorded was less than 15%. Diaphragm dysfunction was also suggested by low amplitude of the diaphragmatic compound muscle action potential in each patient.

Conclusion: Diaphragm dysfunction, secondary to lower motor neuron loss, was mirrored by the low amplitude of the diaphragm CMAP in the 3 patient case reports. These cases suggest that a thickening fraction $\leq 15\%$ is associated with severe diaphragm weakness and risk of respiratory failure.

Significance: Before appropriate data obtained in a population of ALS patients are available, we propose DTf (%) $< 20\%$ as a possible indicator of diaphragm dysfunction in ALS patients.

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1. Introduction

The most common acquired motor neuron disease is Amyotrophic Lateral Sclerosis (ALS) with a global incidence of 1–2.6 per 100,000 individuals (Talbot et al., 2016). With the identification of the role of many genes in the pathogenesis, it is no longer exclusively sporadic. The average duration of the disease can be quite variable, but usually 3–5 years from the symptom onset (Tiryaki and Horak, 2014). Respiratory failure is the most common cause of death in these patients (Tiryaki and Horak, 2014, de Carvalho et al., 2019, Similowski et al., 2000, Noda et al., 2016).

The diaphragm is the major inspiratory muscle that gets involved, resulting in weakness or impairment of the normal respiration (de Carvalho et al., 2019). Severe loss of motor units in the muscles is the etiology behind the diminished respiratory capacity in ALS patients (de Carvalho et al., 2019). Diaphragmatic weakness is secondary to the involvement of phrenic motor neurons in ALS seen in the patients with mean disease duration of 20–22 months (Similowski et al., 2000).

Usually, clinical symptoms coupled with pulmonary function tests, phrenic nerve stimulation, pulse oximetry, arterial blood gases (ABG), capnography and electromyography are utilized to assess the weakness of diaphragm and the respiratory capacity. In about 3% of ALS patients, ventilatory insufficiency is the presenting symptom (Sarwal et al., 2013).

Recently ultrasonographic measurement of diaphragmatic thickness and its correlation with diaphragm CMAP and pulmonary function tests is described (Noda et al., 2016). Yet it lacks universally agreed-upon standardized values in ALS patients. The lower

Abbreviations: DTf, Diaphragmatic thickening Fraction; ALS, Amyotrophic Lateral Sclerosis; ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC, Forced Vital Capacity; CMAP, Compound Muscle Action Potential.

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limit of normal diaphragm CMAP is 0.45 mV (Resman-Gašperšič and Podnar, 2008).

The thickness of the diaphragm can be measured the best at the zone of apposition-ZA (Wait et al., 1989, Fayssoil et al., 2018, Pinto et al., 2016). ZA is an area of the chest wall where abdominal contents and rib cage are in proximity. High-resolution linear US probe of 10 MHz (Philips Healthcare EPIQ 7 Ultrasound System Inc.) was used to measure the diaphragm thickness (DT) using B mode. The probe was positioned between the antero-axillary and mid-axillary lines, perpendicular to the chest wall (Wait et al., 1989, Fayssoil et al., 2018, Sarwal et al., 2013).

With B mode, the hemi-diaphragm was identified beneath the intercostal muscles as a hypo-echogenic layer of muscle tissue located between two hyper-echogenic lines (the pleural line and the peritoneal line) (Wait et al., 1989, Fayssoil et al., 2018, Sarwal et al., 2013). Fig. 1 shows the B-mode ultrasound image of the left hemi diaphragm during active inspiration and expiration.

The Diaphragmatic thickening measured as DT is the difference between DT_i and DT_e, [at the end of inspiration (DT_i) and expiration (DT_e)] (Samanta et al., 2017). The Diaphragm thickening fraction-DTf (%) was calculated as the difference between DT_i and DT_e divided by DT_e × 100 (Wait et al., 1989, Samanta et al., 2017).

Diaphragm thickening fraction (DTf) less than 20% is a measure of ultrasonographic diaphragmatic dysfunction in patients on mechanical ventilation (Jung et al., 2016). The role of DTf as a predictive tool for extubation was studied in these patients extensively (Jung et al., 2016). Herein, we report three cases of ALS where DTf measurement was utilized to determine the diaphragm dysfunction.

2. Cases

2.1. Case 1

A pulmonologist saw a 55-year old woman with a history of hypertension, hyperlipidemia, and stroke with residual right-sided hemiparesis for dyspnea and orthopnea. Her forced vital capacity (FVC) was 45% of predicted, and chest CT was normal. The patient referred to the electro diagnostic lab for phrenic nerve studies. Left phrenic motor nerve compound motor action potential was 0.2 mV and right was 0.1 mV.

We noticed diffuse fasciculations during these studies, and upon further questioning, she complained of progressive weakness in the upper limbs and she was referred to a neurologist for the same. In the neurology clinic, she reported the history of weakness of the right upper limb causing her to drop things for the last two years. The patient underwent electromyography, which showed diffuse denervation in all body regions and satisfied criteria for ‘probable ALS disease with lab evidence’ ALS based on modified El Escorial criteria (Wijesekera and Leigh, 2009). The Amyotrophic lateral sclerosis functional rating scale- revised (ALSFRS-R) was 38

(Bakker et al., 2017). The thickening fraction of the right diaphragm was 10%, and that of the left was 15%.

2.2. Case 2

A 65-year-old man with a history of hypertension, type 2 diabetes mellitus, and peripheral neuropathy, was seen by a pulmonologist for orthopnea and dyspnea. He underwent chest CT, cardiac echo and catheterization, which were normal. His forced vital capacity (FVC) was 45% of predicted, and he was referred to the electrodiagnostic lab for phrenic nerve studies. Diaphragm compound muscle action potential was 0.2 mV bilaterally. Similar to case 1, we noticed diffuse fasciculations and on examination split hand sign was positive. The neurologist saw him in the clinic where eliciting further history revealed the progressive weakness of the upper limbs (right worse than left). He endorsed difficulty lifting arms. The patient underwent electromyography, which showed diffuse denervation in all body regions and satisfied criteria for ‘Probable ALS disease with lab evidence’ on the El Escorial criteria. The ALSFRS-R was 40. DTf (%) measured by using a high-resolution linear US probe using B-mode was 15% bilaterally.

2.3. Case 3

A 53-year-old woman diagnosed with lower limb onset ALS presents to the neurology clinic with worsening of shortness of breath. She initially presented with a history of recurrent falls and is ambulant with the help of a walker. She has neuropathy secondary to chronic use of alcohol.

She underwent studies to determine the respiratory function, and the forced vital capacity (FVC) was 40% of predicted and phrenic nerve compound muscle action potential was 0.1 mV on the right and 0.2 mV on the left. Her ALSFRS-R score was 35 and DTf (%) measured using a high-resolution linear US probe using B-mode was 10% bilaterally.

Table 1 summarizes the compound muscle action potential, pulse oximetry, capnography and thickening fraction in all three patients along with ALSFRS-R scores.

3. Discussion

Marked loss of the motor units of diaphragm eventually leads to the weak inspiratory strength in ALS patients and compromised respiratory capacity causing respiratory failure (de Carvalho et al., 2019). Volitional tests like standard respiratory function tests/spirometry are cumbersome to perform due to facial muscle weakness, especially in the bulbar onset ALS. Air leak around the mouthpiece makes these tests unreliable (de Carvalho et al., 2019).

Although measurement of the compound muscle action potential (CMAP) of the diaphragm is reliable, inaccurate electrode placement can interfere with reproducibility of the result and patient needs to endure multiple electric shocks, which is uncomfortable. Noda et al. studied the utility of ultrasound in evaluating the diaphragm dysfunction in neuromuscular diseases (43% of

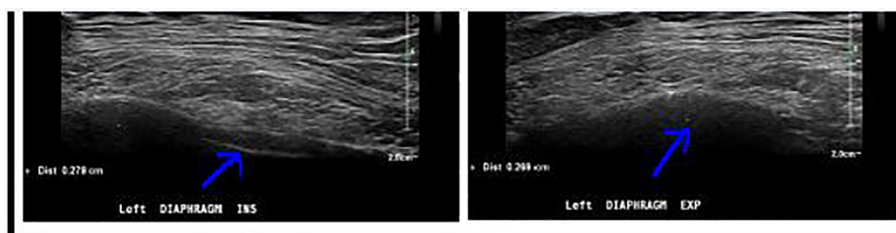


Fig. 1. B-mode ultrasound image of the hemi-diaphragm- arrow depicts hypo-echogenic diaphragm.

Table 1

The table summarizes the compound muscle action potential, pulse oximetry, capnography, and diaphragm thickening fraction in all three patients along with ALSFRS-R scores and their normal range.

	Case 1	Case 2	Case 3	Normal reference
Phrenic nerve motor nerve CMAP	0.1 mV (right) 0.2 mV (left)	0.2 mV (right) 0.2 mV (left)	0.1 mV (right) 0.2 mV (left)	normal 0.45 mV
ALSFRS-R	38	40	35	48 = best
Pulse Oximetry	98 mmHg	96 mmHg	96 mmHg	75–100 mmHg
Capnography	50 mmHg	52 mmHg	48 mmHg	35–45 mmHg
Thickening Fraction (DTf)%	10% (right) 15% (left)	15% (right) 15% (left)	10% (right) 10% (left)	

Notes: CMAP: Compound Muscle Action Potential; DTf(%): Diaphragm thickening fraction percentage; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; Pulse oximetry values in mmHg; Capnography values in mmHg.

them with ALS) (Noda et al., 2016). They concluded that it could be used objectively to evaluate respiratory dysfunction. Previously, M-mode ultrasound has been used where diaphragmatic excursions were only measured, which was replaced by B-mode, which enables us to obtain the anatomic information of the muscle as well (Noda et al., 2016).

There is a wide variation in diaphragm thickness measured by [Wait et al: 2.2±0.4 mm; Ueki et al: 1.7±0.2 mm; Boon et al: 3.3±1 mm (right), 3.4±1.8 mm (left)] and there are no widely accepted values for diaphragm dysfunction in ALS patients (Faysoil et al., 2018; Boon et al., 2013).

The leading cause of weaning failure in mechanically ventilated patients is diaphragmatic dysfunction due to polyneuropathy and myopathy secondary to critical illness (Theerawit et al., 2018, Jung et al., 2016, Zambon et al., 2017). Recently the role of diaphragm ultrasound has been extensively studied in these patients, and the utility of thickening fraction in predicting the success of weaning outcome has also been reported (Theerawit et al., 2018, Jung et al., 2016).

Jung et al. in their study reported that diaphragmatic thickening fraction (DTf) of 20% was a substitute of diaphragm dysfunction and DTf of 30% considered as a substitute to predict the success of weaning (Jung et al., 2016). Zambon et al. in their study determined that the respiratory muscle workload estimate and the prediction of extubation outcome during spontaneous breathing trial best estimated by calculating thickening fraction. DTf of 30 – 36% reported as a cut off to predict extubation success or failure (Zambon et al., 2017).

Diaphragm dysfunction in ALS has a similar mechanism of the secondary nerve (phrenic), and muscles (diaphragm) dysfunction due to death of anterior horn cell and DTf (%) might serve as a useful surrogate marker even in ALS.

In all our three ALS patients, DTf (%) of <20% was predictive of severe diaphragm dysfunction as measured by phrenic nerve conduction studies. By using a cut-off ratio as compared to absolute values, we reduce the variability from patient to patient or even operator to operator thus making it a more useful tool to assess diaphragm dysfunction on a larger scale as well as serially in the same patient. In our report of three ALS patients, we showed the correlation between low DTf and diaphragm dysfunction. Larger studies are needed to see if DTf (%) of less than 20% can be reproducible as a marker of diaphragm dysfunction in ALS patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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