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The impact of Diaphragmatic Dysfunction assessed by chest ultrasound on noninvasive ventilation outcome in patients with acute exacerbation of chronic obstructive pulmonary disease.

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Abstract:

Background: Noninvasive ventilation (NIV) is now seen as first-line treatment in patients with acute exacerbation of chronic obstructive pulmonary disease and respiratory acidosis (AECOPD). Therefore, the identification of the predictive factors of NIV failure could assist clinicians in detecting the patients at greater risk of negative outcomes. One of these factors is the diaphragmatic dysfunction (DD). Although the measurement of trans-diaphragmatic pressure is the gold current standard for assessing diaphragmatic function, ultrasonography (US) of the diaphragm at the bedside is capable of identifying (DD) in several clinical conditions. **Objectives:** to evaluate the prevalence of diaphragmatic dysfunction (DD) during AECOPD, and its impact on NIV outcome.

Setting: Department of Chest, Respiratory intensive care unit (ICU), Beni-Suef University Hospital. **Methods:** a prospective observational study which was conducted on 41 adult patients with acute exacerbation of chronic obstructive pulmonary disease who were admitted to respiratory ICU of chest department Beni-Suef University hospital for NIV. The cases underwent diaphragmatic assessment by bedside diaphragmatic ultrasound. Diaphragmatic thickness fraction (DTF) was calculated from the following formula: (Diaphragmatic thickness at end inspiration – Diaphragmatic Thickness at end expiration)/ Diaphragmatic Thickness at end expiration. NIV outcomes (failure and success groups) was analyzed to find a cutoff point of DTF to predict success of NIV. **Results:** The prevalence of diaphragmatic dysfunction in all studied patients was 18 patients (43.5%) out of 41 patients most of them were among NIV failure group [12 (70.5%) out of 17 patients]. The cut off point of DTF was below 0.306 to predict failure of NIV . with a P value 0.002. **Conclusions**: Assessment of DTF by diaphragm ultrasound in B-mode represents an easy to-obtain new index for prediction of success or failure of NIV in AECOPD patients needing NIV.

Keywords: Diaphragmatic dysfunction, Noninvasive ventilation, Respiratory failure, Chest Ultrasound.

1. Introduction:

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (1).

NIV is now seen as first-line treatment in patients with AECOPD and respiratory acidosis (2), as it decreases the need for endotracheal intubation and improves survival rate.

Therefore, the identification of the predictive factors of NIV failure could assist clinicians in detecting the patients at greater risk of negative outcomes. Factors identifying the patients requiring endotracheal intubation after a short course of NIV have not been fully elucidated (3). During severe AECOPD, progressive development of dynamic hyperinflation causes a change in the geometry of the chest wall and diaphragm, with shifting the tidal breathing closer to the individual's total lung capacity. 2.

As such, the generation of higher pressure levels by the respiratory muscles is required to maintain tidal volume (Vt), thus exposing the diaphragm to dysfunction and, subsequently, to fatigue. In addition other factors may contribute to the development of diaphragmatic dysfunction (DD) during AECOPD, including an unfavorable energy 3.

balance enhanced systemic inflammation, oxidative stress, acute hypercapnia and acidosis (4).

Although the measurement of trans-diaphragmatic pressure is the gold current standard for assessing diaphragmatic function, ultrasonography (US) of the diaphragm at the bedside is capable of identifying DD in several clinical conditions (5).

In this study we evaluated the prevalence of diaphragmatic dysfunction (DD) during AECOPD, and its impact on NIV outcome.

2. Patients and Methods:

A prospective observational study was conducted on forty one adult patients with acute exacerbation of COPD (AECOPD) who were admitted to respiratory ICU of chest department Beni-Suef University hospital for acute hypercapnic respiratory failure with acidosis needing noninvasive ventilation (NIV) From January 2019 to July 2019.

2.1 Inclusion criteria:

1. Patients more than 18 years of both gender.
2. Patients who were admitted with AECOPD with hypercapnic respiratory failure and needed NIV; according to GOLD 2019; [Persistent acidosis (pH <7.35), hypercapnia ($PaCO_2$ >49 mmHg) or tachypnea (respiratory rate >22 breaths per minute) despite optimal bronchodilator and controlled oxygen therapy (6).

2.2 Exclusion criteria:

1. Patients presented with acute pulmonary edema.
2. The coexistence of interstitial lung disease.
3. Previously diagnosed diaphragmatic palsy.
4. Pregnancy.
5. Patients who needed immediate endotracheal intubation.
6. Shock or severe hemodynamic instability.
7. History of neuromuscular disease, chest wall deformities.
8. Patients with chest wall lesions that may prevent use of chest ultrasound e.g ; burn and open wound.
9. Patients with pneumothorax or traumatic lung injury.
10. Patients with any contraindication of NIV as facial burns, copious respiratory secretions….. etc.
12. Patients refusing to be enrolled in our study.

2.3 All patients were subjected to:

1. Full history taking from the patients' close relatives
2. Full clinical examination including general and chest examination
3. Routine labs. were done as ABGs, CBC, AST,ALT, Bilirubin, Urea, Creatinine, coagulation profile, Na, K, Random blood sugar and other laboratory investigations when needed.

ABGs was done on admission and after two hours of using NIV and then serially at day one and with increasing interval on improvement of the patient's condition.

4. Chest X-ray.

5. NIV treatment:

NIV was started without sedated and via a face mask connected to a high performance ventilator (Drager medical GmbH, 23542 Lubeck, Germany) in pressure support mode. External positive end-expiratory pressure was initially set to 5 cmH_2O and subsequently increased according to clinical parameters and ventilator waveforms.

Pressure support was set to 10 cmH_2O initially then progressively increased, according to Vt, MV, and waveforms in order to obtain a Vt of 6–8ml/kg and a respiratory rate of < 30 breath/min. The fraction of inspired oxygen (FiO_2) was increased to achieve a transcutaneous saturation of 88–94%. The setting was adjusted by the attending physician on the basis of blood gases and/or continuous pulse oximeter. NIV was delivered as long as possible on day 1, then for16 h/day (including 6-8 hrs overnight) and 12 h/day on days 2 and 3, respectively. NIV was then discontinued according to clinical improvement or deterioration. Patients who failed to improve on NIV were switched to invasive ventilation. The decision was made by the attending physician according to recommendations **(6),** but blinded to the result of the assessment of diaphragmatic function.

6.Ultrasound assessment:

Ultra-sonographic assessment of the diaphragm using (Hitachi ALOKA, Model F31, Japan) was performed on admission before starting NIV in lung/chest US evaluation.

Motility of the diaphragm (**Diaphragmatic excursion**) was assessed by a B-mode US device at the bedside connected to a lower frequency curvilinear transducer (2 to 6 MHz). Measurements were performed with the patient in semi setting with an average inclination of 45 degrees. The position of the probe was placed between the mid-clavicular and anterior axillary lines, in the anterior subcostal region. The transducer was directed medially, cranially, and dorsally, so that the ultrasound beam reached the posterior third of the right diaphragm approximately 5 cm lateral to the inferior vena cava foramen. B mode was used to visualize the diaphragm moving towards or away from the transducer. Then M mode was used with the line of sight positioned in order to obtain maximum excursion. Amplitude of excursion was measured, directly by measuring the amplitude of excursion of the diaphragm on the vertical axis of the M mode ultrasound tracing. Measurement were taken on tidal and deep breathing.

Diaphragmatic thickness

Two-dimensional B-mode ultrasound was used to measure diaphragm thickness at the zone of apposition during inspiration and expiration using the intercostal approach**.** Obtained through an intercostal view, a higher frequency linear array transducer (7 to 18 MHz) was placed at the anterior axillary line, with the transducer positioned to obtain a sagittal image at the intercostal space between the 7th and 8th, or 8th and 9th ribs. An image spanning 2 ribs, with the intercostal space between the ribs was ideal. In this view, the zone of apposition was assessed for measurements such as diaphragm thickness and echogenicity.

The diaphragm was imaged as a structure formed of two echoic lines (the diaphragmatic pleura and the peritoneal membrane) and a hypoechoic structure between them (the muscle itself)). Several images of the diaphragm were captured during quiet tidal breathing, including at least three at the point of end of inspiration and at least three at end of expiration. On each B-mode image, the diaphragm thickness (Tdi) was measured from the middle of the pleural line to the middle of the peritoneal line. The average of these three measures was taken. The measurement of thickness alone may miss an acutely paralyzed diaphragm with normal thickness and could incorrectly identify atrophy in a low weight individual with a healthy, yet thin. Therefore, the degree of diaphragm thickening has been proposed to be more sensitive than measurement of thickness alone **(5)**.So the diaphragmatic thickness fraction (DTF) was calculated from the following formula: [(Diaphragmatic thickness at end inspiration − Diaphragmatic thickness at end expiration)/ Diaphragmatic thickness at end expiration]. Almost all measurements concerning DE or DTF at the current study was performed at the right side as on left side the window of view was very poor and difficult to obtain.

According to NIV outcome we divided our studied patients into:

- Group I: group of successful outcome of NIV.
- Group II: group of failure outcome of NIV.

Statistical methodology

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Shapiro Wilk test. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing normally distributed data and Mann Whitney *U* test for independent samples for comparing not-normal data. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for DTF in predicting failure of NIV. Two tailed *p* values less than 0.05 was considered statistically significant. Univariate and multivariate logistic regression analysis of the factors affecting the failure of NIV was done to screen out the independent risk factors for NIV failure. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

3. Results:

The study included 41 patients who were eligible with the study protocol, after informed consent was obtained from first of kin relative. Bed side ultrasonography of the diaphragm was done to those patients before applying NIV.

Data from clinical history, investigations and examination and diaphragmatic parameters measured by ultrasound were collected and analyzed in relation to NIV outcomes.

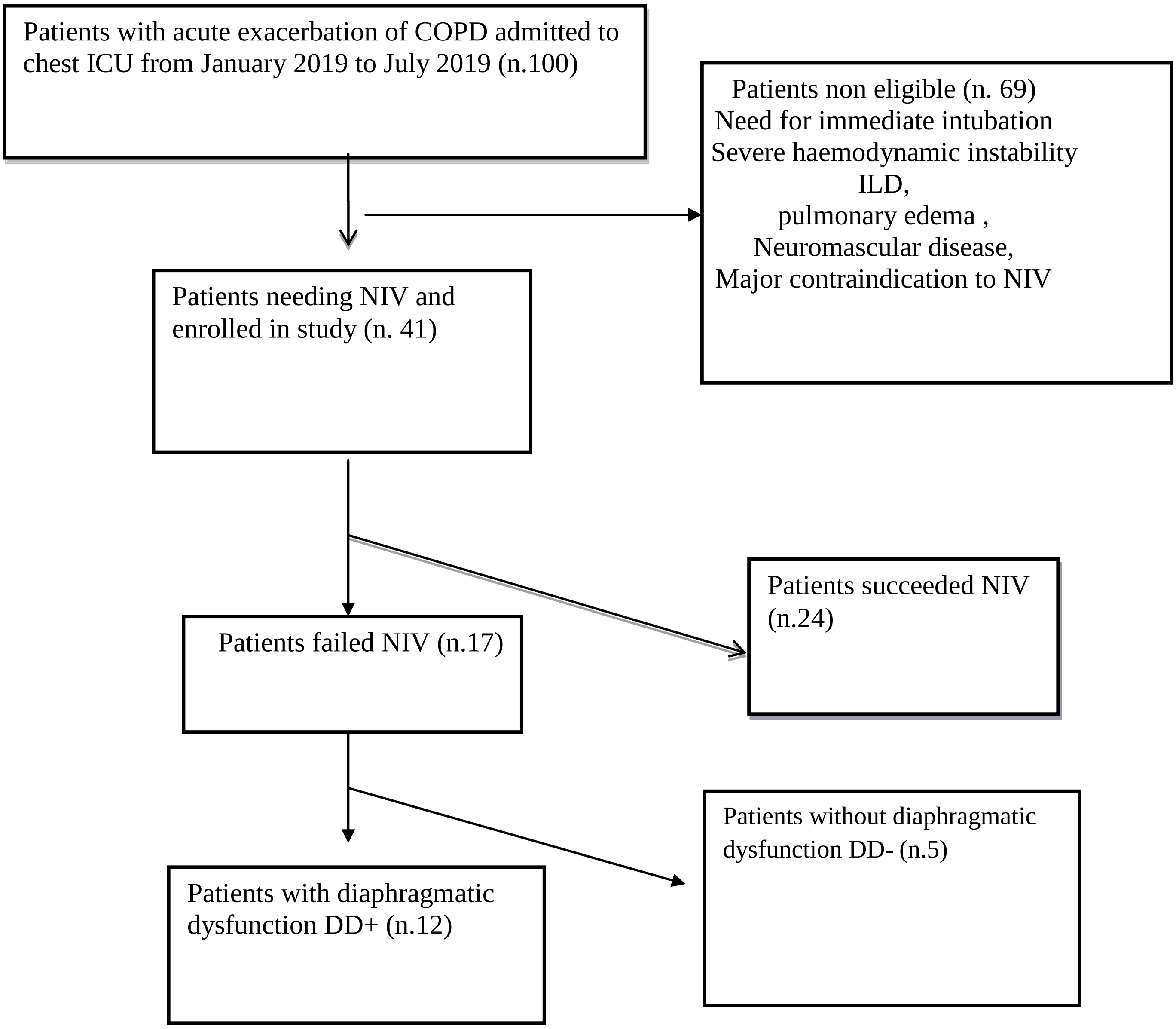

Figure (1) Diagram illustrating data flow of studied patients

Table (1) Baseline characteristics of the study population as a whole and according to failure or success of NIV

Patients features	All studied patient	Group I	Group II	p value
Number and percent	41 (100%)	24(58.5%)	17(41.5%)	
Age years	63.9(45-85)	63.9(45-85)	68.1(45-85)	0.223
Male sex	30, 73.2%	16, 66.7%	14, 82.4%	0.309
Smoking	28, 68.3 %	14, 58%	14, 82.4%	0.029*
Prev. hospital admission	35, 85.4 %	18, 75 %	17, 100 %	0.033*
Prev. mechanical ventilation	15, 36.6%	8, 33.3 %	7, 41.2%	0.861
Prev. NIV	15, 36.6%	9, 37.5%	6, 35.3%	0.861
Prev. steroid use	10, 24.4%	3, 12.5%	7, 41.2%	0.533
Prev. theophylline use	24, 58.5%	12, 50 %	12, 70.6%	0.160
Comorbidities	25, 61 %	18, 75%	7, 41.2%	0.031*
Pneumonia	14, 34.1%	5, 20.8%	9, 52.9%	0.036*

Table (2) Comparative statistical analysis between group I (success group) and group II (failure group) regarding diaphragmatic parameters measured by ultrasound

Variable	Group I (mean ± SD) (n)24	Group II (mean ± SD) (n)17	P value
Average inspiratory thickness (cm)	0.9 ± 0.38	0.9 ± 0.28	0.854
Average expiratory thickness(cm)	0.62 ± 0.28	0.7 ± 0.17	0.324
DTF	0.5 ± 0.29	0.3 ± 0.13	0.003*
Diaphragmatic excursion in	1.6 ± 0.6	1.4 ± 0.47	0.451

quite breathing (cm)			
Diaphragmatic excursion in deep breathing (cm)	2.6 ± 1.1	2.5± 0.7	0.935

ROC curve analysis for DTF as an index of success or failure from non invasive mechanical ventilation

Table (3) ROC curve for DTF as an index for failure of NIV.

	AUC	Cut off point	Sensitivity	Specificity	PPV	NPV	P value
DTF	0.762	0.306	70.5%	79.1%	70.59	79.17	**0.005***

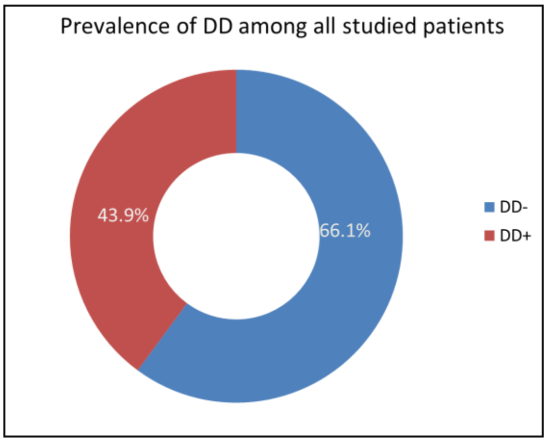

Figure (2): Prevalence of diaphragmatic dysfunction (DD) among all studied patients

Table (4) Comparative statistical analysis between (DD- and DD+) among failure group of NIV.

Variables	DD-	DD+	P value
Failure of NIV(n.17)	5, 29.5%	12 , 70.6%	0.002*

Table (5) Univariate regression analysis of the factors affecting the failure of NIV

Variables	P value
Comorbidity	0.022*
Smoking	0.028*
Previous hospital admission	0.019*
Pneumonia	0.022*
DTF	0.003*

Multivariate Logistic Regression Analysis for NIV Failure:

Variables which were significantly different between failure patients and success patients were employed to carry out multivariate regression analysis, so as to screen out the independent risk factors for NIV failure. Results showed that DTF, smoking and pneumonia were independent risk factors for NIV failure in AECOPD patients**.**

Table (6) Multivariate analysis of the risk factors for noninvasive ventilation failure

Variables	OR and 95%CI	P value
Smoking	**4.95 (1.18,20.84)**	**0.029***
Pneumonia	**22 (1.5, 315.8)**	**0.023***
DTF	**0.001 (0.000,1.24)**	**0.05**

4. Discussion:

The study of 41 patients aged 45 to 85 years with a mean age 63.9 with acute exacerbation of COPD needing NIV showed that:

Regarding factors which have relationship with failure of NIV: There was statistically significant relation between failure of NIV and comorbidity (P value = 0.031). In the same context with **Haji** et al., **(8)** who found that the Percentage of IHD and DM among the failed weaning group was higher than that of the successful weaning group with (P-value= 0.01) and (P- value= 0.03) respectively.

In the current study there were a statistically significant relation between failure and smoking and history of previous hospital admission (P value = 0.029 and 0.033 respectively) and there was a significantly higher incidence of pneumonia within group II 52.9% (n.9) in comparison to group I 20.8% (n.5) (P value = 0.036). Also, a study done by **Shaheen et al., (9)** they found that pneumonia higher in the group NIV failure vs the succeeded group was 33.3% and 10.5% respectively but without significant P value = 0.234.

In the current study there was a statistically significant difference between the failure and succeeded groups of NIV outcome regarding DTF (P value = 0.003).

In agreement with **Farghaly and Hasan (10)** found that DTF was significantly different between patients who had succeeded and those who had failed extubation with p value 0.036 and 0.021 respectively**.**

Regarding optimal cut-off point of DTF for being a predictor successful NIV:

We found that a value ≥ 0.306 was related to successful NIV with a sensitivity of 70.5 % and a specificity of 79.1% and with a PPV value of 70.59 and a NPV 79.17.

In the same context; **DiNino et al., (11)** DTF%≥30% was determined as a predictor for extubation success with 88% sensitivity and 71% specificity. Another study by **Agmy et al., (12)** stated that DTF % > 40% was associated with a successful SBT with a sensitivity of 88% and a specificity of 92%.

The prevalence of diaphragmatic dysfunction (DD+) in all studied patients was 18 patients (43.9%) out of 41 patients mostly among failure group (n.17) was 12 patients (70.5%) with P value 0.002.

Similarly **Marchioni et al., (13)** found that the prevalence of DD among the studied patients with AECOPD (n.75) was 24 patients (32%). Within the failure group (n.26) there were 18 (75%) patients had diaphragmatic dysfunction (DD+), while 8 (16%) patients didn't had (DD-).

5. Conclusion and Recommendations:

Sonographic assessment of DTF may predict success or failure of NIV, this may help clinicians to identify patients with AECOPD at major risk for a negative prognosis. Ultrasound of the diaphragm is a simple method useful to evaluate the thickness of the diaphragm in the zone of apposition. This technique is highly feasible and non-invasive.

Routine examination of diaphragm function by US should be done in every AECOPD patient using NIV as a predictor parameter of successful weaning from NIV.

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