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Ultrasonographic Assessment of Diaphragmatic Function and Its Correlation with Chronic Obstructive Pulmonary Disease Severity

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ABSTRACT

Background: chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world, and it is projected to be the third leading cause of death by 2020. More than 3 million people died because of COPD in 2012, accounting for 6% of all deaths globally.

Objective: the aim of this study is to assess the diaphragmatic function in COPD patients using the ultrasonographic technique, and to study its correlation with severity of the disease.

Patients and Methods: this study was carried out during the period from November 2018 to June 2019, on sixty patients with clinically stable chronic obstructive pulmonary disease (COPD), during their follow up in the outpatient clinic of Chest Department, Bab-Al-Sha'reia University Hospital.

Results: thickness of the diaphragm (TD) at different lung volumes and capacities (RV, FRC and TLC) estimated by U/S, was found to be progressively decreased with increasing COPD severity. TD was found to be decreased significantly in COPD patients when compared with controls. The only exception was the presence of a non-significant relationship between TDRV in control and mild COPD groups, which may denote that diaphragmatic thickness is not markedly affected in early COPD at low lung volumes.

Conclusion: U/S is a simple, easily learned, non-invasive and reliable method that can be used in assessment of the diaphragmatic function and kinetics. There is a significant negative correlation between diaphragmatic function (assessed by measuring diaphragmatic thickness and excursion through U/S) and COPD severity.

Keywords: Ultrasonographic, Diaphragmatic Function, Chronic Obstructive Pulmonary Disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by incomplete reversible airflow limitation [(1)].

Many factors play vital role in the pathogenesis of COPD including: chronic inflammation, alterations in repair mechanisms, oxidative stress, protease-antiprotease imbalance, airways remodeling, in addition to numerous cellular and mediators involvement [(2)].

Systemic effects of COPD influence its progression, and they include loss of fat-free mass (FFM) and muscle wasting. Long-term administration of steroids (even low doses), used widely in the treatment of COPD, can also contribute to respiratory muscle weakness with wasting of the diaphragm (chief respiratory muscle) [(3)].

Patients affected by emphysematous COPD with loss of FFM and muscle wasting show profound alterations regarding the mass and thickness of the diaphragm. The study of the diaphragm is thus considered a key point in the evaluation of patients with COPD, and several methods are employed such as magnetic resonance scans [(4)], phrenic nerve conduction study [(5)] and invasive assessment of trans-diaphragmatic pressure[(6)].

The use of ultrasonographic (U/S) techniques for the assessment of both diaphragmatic excursion and thickness of the diaphragm (TD) at different lung volumes in healthy and diseased individuals was proposed [(6)].

AIM OF THE WORK

The aim of this study is to assess the diaphragmatic function in COPD patients using the ultrasonographic technique, and to study its correlation with severity of the disease.

SUBJECTS AND METHODS

This study was carried out during the period from November 2018 to June 2019, on sixty patients with clinically stable chronic obstructive pulmonary disease (COPD), during their follow up in the outpatient clinic of Chest Department, Bab-Al-Sha'reia University Hospital. These patients were diagnosed and classified into four groups according to GOLD 2019 as following:

- First group: included 15 patients with mild stage.
- Second group: included 15 patients with moderate stage.
- Third group: included 15 patients with severe stage.
- Fourth group: included 15 patients with very severe stage.

Twenty age and sex matched healthy volunteers, served as a control group, were also included in the study.

Inclusion criteria:

Clinically stable patients diagnosed as COPD according to GOLD guidelines 2019, in different stages of disease severity.

Exclusion criteria:

Subjects were excluded from the study if they had any of the following conditions:

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- Chest diseases other than COPD.
- COPD patients with clinical picture suggesting exacerbation.
- Diseases that can affect diaphragmatic motility directly such as diaphragmatic hernia, or indirectly such as pregnancy, abdominal organomegaly or causes of increased intra-abdominal pressure.
- Generalized muscular or neurological disorders.
- Recent thoracic or abdominal surgery.
- Conditions interfering with good U/S window such as: subcutaneous emphysema, chest wall edema and morbid obesity.
- Severe malnutrition or those with BMI <18 kg/m^2.

Control subjects were selected on the basis of the best matching for the age and sex. They were non-smokers without any known medical disorder.

After taking an informed consent, all subjects were submitted to the following:

(1) Full history taking.

(2) General examination.

(3) Local chest examination.

(4) Routine laboratory investigations.

(5) Arterial blood gases.

(6) Plain chest X- ray (postero-anterior and lateral views).

(7) Pulmonary function tests.

(8) Six minute walk test (6MWT):

- The test was performed according to the **American Thoracic Society**[7] guidelines, on a 30 meters distance flat hard course, with identified turnaround points, three-meters interval measurements marked with colored tape on the floor to facilitate the measurement of the whole walked distance and lastly, 2 chairs were available at both ends of the pace in case the tested subject felt dyspneic and needed to rest.

Technique:

- No warm up was done before the test.
- The patients were asked to rest comfortably for 10 minutes prior to the test, during this time blood pressure and heart rate were measured and potential contraindications e.g. arrhythmias and hypotension were assessed.
- Pulse oximetry was used to determine the arterial oxygen saturation of each patient prior to the test.
- Before the start of the test, each patient was asked to stand up and his/her degree of dyspnea was assessed.
- A stop-watch was prepared for timing the test, with the lap counter to zero and timer to 6 minutes.
- When testing severe and very severe COPD patients, the supervisor walked behind the patients to support them in case of staggering and to prevent falling.
- Standardized phrases on about 30-seconds intervals were applied to encourage patients to complete the test.
- Resting during the test was allowed without stopping the clock. The test was stopped at once if the patient cannot go any further distance, and the covered distance was recorded.
- The test was terminated immediately in case the patient developed chest pain, intolerable dyspnea, staggering, diaphoresis, intolerable cramps, severe pallor, cyanosis or ashen appearance [7].

(9) Ultrasonography of the diaphragm:

- Ultrasound machine (SonoScape - SS1 China) was used to assess the diaphragm thickness at different lung volumes and capacities through the high frequency linear probe (7-12 MHz), as well as the diaphragmatic excursion at TLC through the low frequency curvilinear probe (2-6 MHz).

Techniques:

Patients were examined while they were in the supine position as it is more comfortable to the subject, shows less variability and greater reproducibility during spontaneous respiration and allows better excursion of the diaphragm.

Examination was done to the right hemidiaphragm through the liver window as visualization of the left hemidiaphragm is more difficult because of the presence of the smaller splenic window.

(1) Assessment of diaphragmatic thickness (TD):

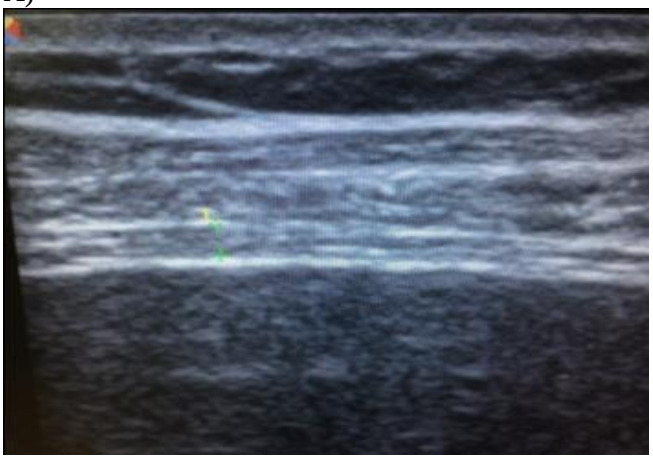
- Measurements were performed at the zone of opposition.
- The examination was performed with a linear probe placed at the anterior axillary line, in the longitudinal plane between 7th and 9th intercostal spaces "intercostal view".
- In B-mode, the diaphragm was visualized as a hypoechoic layer of muscle encased in two hyperechoic layers of connective tissue (the parietal pleura and the peritoneum), deep to the intercostal muscles connecting the two ribs. TD was measured just inside the hyperechoic connective tissue layers [8] during a breath-holding maneuver at the end of forced maximal expiration (corresponding to RV), end of tidal expiration (corresponding to FRC) and maximal inspiration (corresponding to TLC).
  - Two measurements were performed blinded to the result, and the mean value was then reported**.**

(2) Assessment of diaphragmatic excursion:

- The curvilinear probe was placed between the mid-clavicular and anterior axillary lines, in the anterior subcostal region "anterior subcostal view".
- In B-mode the diaphragmatic interface appeared as a hyperechogenic line surrounding the liver. At this point we tilted the probe to obtain the maximum convexity, using the gallbladder, where present as a reference point.
- Imaging was then changed to M-mode with the line of sight positioned in order to obtain maximum excursion.

- The diaphragmatic interface appeared in M-mode as a hyperechogenic line that assumed in time a sinusoidal form with the peak corresponding to maximum inspiration and the trough corresponding to expiration.
- On this M-mode trace, the diaphragmatic excursion was measured as it represented the height of the curve [9].

A)



B)

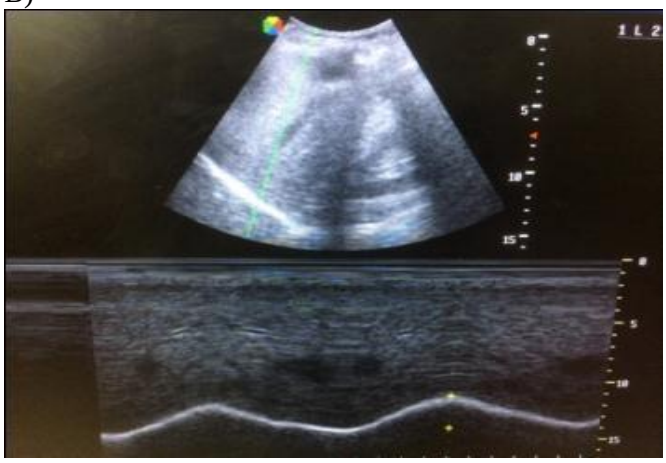


Figure (1): Diaphragmatic ultrasonography of a male patient with moderate COPD
A: diaphragmatic thicknesses at TLC (TDTLC).
B: diaphragmatic excursion.

Ethical approval:
The study was approved by the Ethics Board of Al-Azhar University and an informed written consent was taken from each participant in the study.

Statistical analysis

Data were analyzed using statistical program for social science (SPSS) version 15.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

Probability value (P-value) was interpreted as follow:

- P-value > 0.05 was considered insignificant.
- P-value < 0.05 was considered significant. (*)
- P-value < 0.01 was considered as highly significant. (**)
- P-value < 0.001 was considered as very highly significant. (***)

The following tests were done:

1) **A one-way analysis of variance (ANOVA):** was used when comparing more than two means.
2) **Post-Hoc test:** was used for multiple comparisons among different variables.
3) **Chi-square test:** was used when comparing non-parametric data.

RESULTS

Table (1): Age distribution among studied groups

Group	Mean ± SD	Compared with	p-value
Control	**55.25 ± 5.95**	**Mild COPD**	0.326
		Moderate COPD	0.371
		Severe COPD	0.923
		Very severe COPD	0.97
Mild COPD	**57.47 ± 8.43**	**Moderate COPD**	0.934
		Severe COPD	0.407
		Very severe COPD	0.376
Moderate COPD	**57.27 ± 4.20**	**Severe COPD**	0.455
		Very severe COPD	0.423
Severe COPD	**55.47 ± 5.63**	**Very severe COPD**	0.956

- There are no statistically significant differences (p-values > 0.05) among studied groups as regard age.

Table (2): Diaphragmatic excursion among studied groups

Group	Mean ± SD	Compared with	Post- Hoc test	p-value
Control	**5.94 ± 0.64**	**Mild COPD**	1.38	**< 0.001*** **
		Moderate COPD	1.82	**< 0.001*** **
		Severe COPD	2.27	**< 0.001*** **
		Very severe COPD	2.77	**< 0.001*** **
Mild COPD	**4.56 ± 0.33**	**Control**	-1.38	**< 0.001*** **
		Moderate COPD	0.45	**0.006****
		Severe COPD	0.90	**< 0.001*** **
		Very severe COPD	1.40	**< 0.001*** **
Moderate COPD	**4.12 ± 0.30**	**Control**	-1.82	**< 0.001*** **
		Mild COPD	-0.45	**0.006****
		Severe COPD	0.45	**0.005****
		Very severe COPD	0.95	**< 0.001*** **
Severe COPD	**3.67 ± 0.35**	**Control**	-2.27	**< 0.001*** **
		Mild COPD	-0.90	**< 0.001*** **
		Moderate COPD	-0.45	**0.005****
		Very severe COPD	0.50	**0.002****
Very severe COPD	**3.17 ± 0.32**	**Control**	-2.77	**< 0.001*** **
		Mild COPD	-1.40	**< 0.001*** **
		Moderate COPD	-0.95	**< 0.001*** **
		Severe COPD	-0.50	**0.002****

*** p-value ≤ 0.001 considered very highly significant.
** p-value ≤ 0.01 considered highly significant.

- There are high statistically significant differences between mild and moderate COPD groups, moderate and severe COPD groups and severe and very severe COPD groups as regard diaphragmatic excursion measured by U/S.
- There are very high statistically significant differences among other studied groups.

Table (3): Thickness of the diaphragm at RV among studied groups

	Group	Mean ± SD	Compared with	Post- Hoc test	p-value
RV	**Control**	**1.46 ± 0.26**	**Mild COPD**	0.03	0.607
			Moderate COPD	0.21	**< 0.001*** **
			Severe COPD	0.40	**< 0.001*** **
			Very severe COPD	0.64	**< 0.001*** **
	Mild COPD	**1.43 ± 0.10**	**Control**	- 0.03	0.607
			Moderate COPD	0.18	**0.003****
			Severe COPD	0.37	**< 0.001*** **
			Very severe COPD	0.61	**< 0.001*** **
	Moderate COPD	**1.25 ± 0.05**	**Control**	- 0.21	**< 0.001*** **
			Mild COPD	- 0.18	**0.003****
			Severe COPD	0.19	**0.002****
			Very severe COPD	0.43	**< 0.001*** **
	Severe COPD	**1.06 ± 0.09**	**Control**	- 0.40	**< 0.001*** **
			Mild COPD	- 0.37	**< 0.001*** **
			Moderate COPD	- 0.19	**0.002****
			Very severe COPD	0.24	**< 0.001*** **
	Very severe COPD	**0.82 ± 0.19**	**Control**	- 0.64	**< 0.001*** **
			Mild COPD	- 0.61	**< 0.001*** **
			Moderate COPD	- 0.43	**< 0.001*** **
			Severe COPD	- 0.24	**< 0.001*** **

RV= Residual Volume.

*** p-value ≤ 0.001 considered very highly significant. ** p-value ≤ 0.01 considered highly significant.

- There is no statistically significant difference between control and mild COPD groups as regard thickness of the diaphragm at RV.
- There are high statistically significant differences between mild and moderate COPD groups and moderate and severe COPD groups.There are very high statistically significant differences among other studied groups.

Table (4): Thickness of the diaphragm at FRC among studied groups

	Group	Mean ± SD	Compared with	Post- Hoc test	p-value
FRC	Control	1.85 ± 0.29	Mild COPD	0.22	**0.001*** **
			Moderate COPD	0.43	**< 0.001*** **
			Severe COPD	0.63	**< 0.001*** **
			Very severe COPD	0.83	**< 0.001*** **
	Mild COPD	1.63 ± 0.11	Control	-0.22	**0.001*** **
			Moderate COPD	0.21	**0.003** **
			Severe COPD	0.41	**< 0.001*** **
			Very severe COPD	0.61	**< 0.001*** **
	Moderate COPD	1.42 ± 0.06	Control	-0.43	**< 0.001*** **
			Mild COPD	-0.21	**0.003** **
			Severe COPD	0.20	**0.006** **
			Very severe COPD	0.40	**< 0.001*** **
	Severe COPD	1.22 ± 0.09	Control	-0.63	**< 0.001*** **
			Mild COPD	-0.41	**< 0.001*** **
			Moderate COPD	-0.20	**0.006** **
			Very severe COPD	0.20	**0.006** **
	Very severe COPD	1.02 ± 0.24	Control	-0.83	**< 0.001*** **
			Mild COPD	-0.61	**< 0.001*** **
			Moderate COPD	-0.40	**< 0.001*** **
			Severe COPD	-0.20	**0.006** **

FRC= Functional Residual Capacity.

*** p-value ≤ 0.001 considered very highly significant. ** p-value ≤ 0.01 considered highly significant.

- There are high statistically significant differences between mild and moderate COPD groups, moderate and severe COPD groups and severe and very severe COPD groups as regard thickness of the diaphragm at FRC.
- There are very high statistically significant differences among other studied groups.

Table (5): Thickness of the diaphragm at TLC among studied groups

	Group	Mean± SD	Compared with	Post- Hoc test	p-value
TLC	Control	2.87 ± 0.69	Mild COPD	0.44	**0.001*** **
			Moderate COPD	0.85	**< 0.001*** **
			Severe COPD	1.29	**< 0.001*** **
			Very severe COPD	1.69	**< 0.001*** **
	Mild COPD	2.42 ± 0.22	Control	-0.44	**0.001*** **
			Moderate COPD	0.41	**0.005** **
			Severe COPD	0.85	**< 0.001*** **
			Very severe COPD	1.25	**< 0.001*** **
	Moderate COPD	2.01 ± 0,18	Control	-0.85	**< 0.001*** **
			Mild COPD	-0.41	**0.005** **
			Severe COPD	0.43	**0.003** **
			Very severe COPD	0.83	**< 0.001*** **
	Severe COPD	1.58 ± 1.17	Control	-1.29	**< 0.001*** **
			Mild COPD	-0.85	**< 0.001*** **
			Moderate COPD	-0.43	**0.003** **
			Very severe COPD	0.40	**0.006** **
	Very severe COPD	1.18 ± 0.23	Control	-1.69	**< 0.001*** **
			Mild COPD	-1.25	**< 0.001*** **
			Moderate COPD	-0.83	**< 0.001*** **
			Severe COPD	-0.40	**0.006** **

TLC = Total Lung Capacity.

*** p-value ≤ 0.001 considered very highly significant.

** p-value ≤ 0.01 considered highly significant.

- There are high statistically significant differences between mild and moderate COPD groups, moderate and severe COPD groups and severe and very severe COPD groups as regard thickness of the diaphragm at TLC.
- There are very high statistically significant differences **(p-value < 0.001)** among other studied groups.

Table (6): Thickness of the diaphragm at different lung volumes and capacities in control group

		Post- Hoc test	p-value
RV	**FRC**	-0.39	**0.017***
	TLC	- 1.4	**< 0.001*****
FRC	**RV**	0.39	**0.017***
	TLC	- 1.01	**< 0.001*****
TLC	**RV**	1.403	**< 0.001*****
	FRC	1.01	**< 0.001*****

RV= Residual Volume, FRC= Functional Residual Capacity and TLC= Total Lung Capacity.

*** p-value ≤ 0.001 considered very highly significant.
* p-value ≤ 0.05 considered significant.

- There is a statistically significant difference between thickness of the diaphragm at RV and thickness of the diaphragm at FRC in control group.
- There are very high statistically significant differences between thickness of the diaphragm at TLC and thickness of the diaphragm at RV and FRC in control group.

Table (7): Thickness of the diaphragm at different lung volumes and capacities in mild COPD group

		Post- Hoc test	p-value
RV	**FRC**	-0.20	**0.0016****
	TLC	-1.24	**< 0.001*****
FRC	**RV**	0.20	**0.0016****
	TLC	-1.04	**< 0.001*****
TLC	**RV**	1.24	**< 0.001*****
	FRC	1.04	**< 0.001*****

RV= Residual Volume, FRC= Functional Residual Capacity and TLC= Total Lung Capacity.

*** p-value ≤ 0.001 considered very highly significant.
** p-value ≤ 0.01 considered highly significant.

- There is a high statistically significant difference between thickness of the diaphragm at RV and thickness of the diaphragm at FRC in mild COPD group.
- There are very high statistically significant differences between thickness of the diaphragm at TLC and thickness of the diaphragm at RV and FRC in mild COPD group.

Table (8): Thickness of the diaphragm at different lung volumes and capacities in moderate COPD group

		Post- Hoc test	p-value
RV	**FRC**	- 0.17	**0.013***
	TLC	- 0.76	**< 0.001*****
FRC	**RV**	0.17	**0.013***
	TLC	- 0.59	**< 0.001*****
TLC	**RV**	0.76	**< 0.001*****
	FRC	0.59	**< 0.001*****

RV= Residual Volume, FRC= Functional Residual Capacity and TLC= Total Lung Capacity.

*** p-value ≤ 0.001 considered very highly significant.
* p-value ≤ 0.05 considered significant.

- There is a statistically significant difference between thickness of the diaphragm at RV and thickness of the diaphragm at FRC in moderate COPD group.
- There are very high statistically significant differences between thickness of the diaphragm at TLC and thickness of the diaphragm at RV and FRC in moderate COPD group.

Table (9): Thickness of the diaphragm at different lung volumes and capacities in severe COPD group

		Post- Hoc test	p-value
RV	**FRC**	-0.16	**0.031***
	TLC	-0.52	**< 0.001*****
FRC	**RV**	0.16	**0.031***
	TLC	-0.36	**< 0.001*****
TLC	**RV**	0.52	**< 0.001*****
	FRC	0.36	**< 0.001*****

RV= Residual Volume, FRC= Functional Residual Capacity and TLC= Total Lung Capacity.

*** p-value ≤ 0.001 considered very highly significant.
* p-value ≤ 0.05 considered significant.

- There is a statistically significant difference between thickness of the diaphragm at RV and thickness of the diaphragm at FRC in severe COPD group.
- There are very high statistically significant differences between thickness of the diaphragm at TLC and thickness of the diaphragm at RV and FRC in severe COPD group.

Table (10): Thickness of the diaphragm at different lung volumes and capacities in very severe COPD group

		Post- Hoc test	p-value
RV	**FRC**	- 0.21	**0.026***
	TLC	- 0.36	**< 0.001*****
FRC	**RV**	0.21	**0.026***
	TLC	- 0.15	0.095
TLC	**RV**	0.36	**< 0.001*****
	FRC	0.15	0.095

RV= Residual Volume, FRC= Functional Residual Capacity and TLC= Total Lung Capacity.

*** p-value ≤ 0.001 considered very highly significant.
* p-value ≤ 0.05 considered significant.

- There is no statistically significant difference between thickness of the diaphragm at FRC and TLC in very severe COPD group.
- There is a statistically significant difference between thickness of the diaphragm at RV and thickness of the diaphragm at FRC in very severe COPD group.
- There is a very high statistically significant difference between thickness of the diaphragm at FRC and thickness of the diaphragm at TLC in very severe COPD group.

DISCUSSION

In the present study, the mean ages (in years) of COPD patients showed a statistically insignificant differences among the study groups.

In the current study, 57 COPD patients (95%) were males, and only 3 patients (5%) were females, while 19 controls (95%) were males, and only one control subject (5%) was a female, with a statistically insignificant difference between COPD groups in one hand and the control group in the other hand (p-values > 0.05).

Male majority among COPD patients reported in this study was similar to the results recorded by **Kim *et al.*** [10]. This finding could be explained by the fact that COPD is a male dominant disease, and that the higher percentage in males may be related to the higher prevalence of smoking in this gender and more frequent occupational exposures.

The mean values of BMI (expressed in kg/m^2) were: (27.91 ± 3.52) in mild COPD patients, (26.99 ± 5.96) in moderate COPD patients, (25.09 ± 5.13) in severe COPD patients and (25.41 ± 3.90) in very severe COPD patients, while that of the control group was (27.50 ± 3.82) kg/m^2, with no statistically significant differences (p-value > 0.05) among the study groups.

These results were in agreement with **Vermeeren *et al.*** [11] who found that 73% of COPD patients had normal BMI and normal fat-free mass index (FFMI), and **Vesbo *et al.*** [12] who found that 83.8% of COPD patients had normal or high BMI and FFMI above the 10^{th} percentile. However, they were against those of **Chailleux *et al.*** [13] ***and*** ***Talamo et al.,*** [14] who found a positive correlation between COPD severity and low BMI.

Insignificant differences among studied groups as regard age, gender and BMI supported the reliability of the results of the current study, because the variability of these factors may affect diaphragmatic strength and function. In a study included 164 healthy subjects, **Kantarci *et al.*** [15] reported that females had a statistically significant decreased diaphragmatic motion than male subjects, and that the mean diaphragmatic motion was significantly less in underweight individuals when compared with subjects who were of normal weight, overweight or obese. In addition to previous findings, the same study found that, subjects younger than 30 years of age had a statistically significant decreased diaphragmatic motion, when compared with older subjects up to 60 years. The main conclusion of this study was that sex, BMI and age can affect diaphragmatic motion to some extent.

Seok *et al.* [16] measured the thickness of the diaphragm and the diaphragmatic thickening fraction (DTF) in 80 healthy volunteers using ultrasound, and they concluded that sex, weight, height and BMI significantly affected the thickness of the diaphragm, but they had a little effect on the DTF.

In our study, we found a negative correlation between disease severity and PaO_2, which denotes that the mean PaO_2 value decreased in a progressive manner, while moving from a less severe to a more severe stage of COPD. The mean values of PaO_2 (expressed in mmHg) were: (85.36 ± 4.26) in mild COPD patients, (78.20 ± 5.53) in moderate COPD patients, (73.85 ± 4.26) in severe COPD patients and (69.17 ± 2.12) in very severe COPD patients, while that of the control group was (87.75 ± 1.95) mmHg, with high statistically significant differences among all studied groups, except between control and mild COPD groups in which a non-significant relationship exist.

These results matched with those of **Kim *et al.*** [10] and **Kent *et al.*** [17] who documented that, with deterioration of pulmonary function and disease progression, the risk of alveolar hypoxia and consequent hypoxemia increase. The possible explanation of reduced PaO_2 is due to ventilation/perfusion (V/Q) mismatch. This V/Q mismatch is measurable, even in subjects with mild COPD, but it appears to increase with the progression of disease.

There were no statistically significant differences among the studied groups as regard pH, $PaCO_2$ and HCO_3. This could be explained by the selection of non-exacerbating stable COPD patients, with total exclusion of patients who were in respiratory failure.

These results merged with those of **Elbehairy *et al.*** [18] who concluded that no statistically significant differences were present between patients with mild COPD and healthy subjects during rest as regard pH, PO_2, PCO_2, SO_2 and HCO_3.

In the current study a very highly significant negative correlation between 6MWD and the severity of COPD was observed, as well as a very highly significant decrease in 6MWD in COPD patients when compared with the healthy subjects.

The mean values of 6MWD (expressed in meters) were: (550.67 ± 35.14) in mild COPD patients, (501.53 ± 23.56) in moderate COPD patients, (409.13 ± 32.21) in severe COPD patients and (319.13 ± 27.56) in very severe COPD patients, while that of the control group was (662.30 ± 48.86) m.

Our recorded 6MWD in healthy group was close to the figure reported by **Mishra and Sinha** [19], who found that the mean 6MWD in healthy individuals was (626.69 ± 64.67) m, and not far from (698 ± 96) m

which is the distance registered by **Gibbons *et al.* [20]** in a study of multiple repetition 6-minute walk test in healthy adults older than 20 years.

This great differences in recorded 6MWD among studies, could be referred to the variations in age, race, ethnicity and several demographic and anthropometric factors which were shown to influence 6MWD. One other possible interpretation for the wide gap among researches is the absence of test repetition in most of studied, as test repetition provides familiarization of the subject with the procedure and influences the 6MWD.

They also matched with the findings of **Chen *et al.* [22]**, who recorded 6MWD for 150 COPD patients in different stages of severity, and found that the mean values in meters were: (548.5 ± 37.0) in mild COPD, (505.3 ± 46.2) in moderate COPD, (421.7 ± 45.3) in severe COPD and (321.9 ± 30.6) in very severe COPD. These results proved that, as the airflow limitation progress, the exercise tolerance of the patients is impaired more and more seriously.

These results came in agreement with those of **Ong *et al.* [23]** and **Sarioglu *et al.* [24]** who showed that the BODE index was a significant determinant for the severity of COPD with respect to FEV1values, and it was found to be related to the annual rate of hospitalizations and emergency visits.

In the present study diaphragmatic excursion was found to be negatively correlated with the severity of COPD, with the least ultrasonographic measurements in patients with very severe disease, at the same time healthy control subjects showed a significant higher diaphragmatic excursion than all COPD groups.

The mean values of diaphragmatic excursion at TLC (expressed in centimeters) were: (4.56 ± 0.33) in mild COPD patients, (4.12 ± 0.30) in moderate COPD patients, (3.67 ± 0.35) in severe COPD patients and (3.17 ± 0.32) in very severe COPD patients, while that of the control group was (5.94 ± 0.64) cm.

They also agreed with **Paulin *et al.* [25]** who found that negative correlation was found between diaphragmatic mobility and the perception of dyspnea in patients with COPD, indicating that changes in the position of the diaphragm make ventilation difficult, reducing respiratory capacity and increasing the sensation of dyspnea.

TD was found to be decreased significantly in COPD patients when compared with controls at different lung volumes and capacities. The only exception was the presence of a non-significant relationship between TDRV in control and mild COPD groups, which may denote that diaphragmatic thickness is not markedly affected in early COPD at low lung volumes.

On the other hand, the mean values of TDRV, TDFRC and TDTLC of COPD groups in this study were at wide distance from those reported in a recent study conducted by **Abd El-Aziz *et al.* [26]**, in which 60 COPD patients with different stages of severity were involved.

The differences among various studies concerned with ultrasonographic diaphragmatic measurements, especially diaphragmatic thickness, may be attributed to many reasons, including ethnic background of subjects, poor acoustic window in up to 10% of population or factors related to the ultrasound devices and techniques**[27].**

Lastly, in our work we compared the mean values of thickness of the diaphragm at different lung volume and capacities (RV, FRC and TLC) for each studied group, and we found statistically significant relationships, with the only exception (a non-significant relation) between thickness of the diaphragm at FRC and TLC in very severe COPD group.

This later finding was merged with the results of **Jamaati *et al.* [28]**, who reported a mean TLC for their studied 50 patients (among whom 32% were severe COPD patients and only 4% had very severe disease) to be 6.9128 ± 1.96403 L, and a mean FRC for them to be 5.7803 ± 1.99386 L, with FRC/TLC ratio 83.6%.

Hence, this non-significant relation could be explained by the very high FRC/TLC ratio in patient with very severe COPD, which may exceed 90%, as well as the extremely weak diaphragm in such patients, which failed to thickened adequately with changes in lung volumes.

CONCLUSION

- Ultrasonography is a simple, easily learned, non-invasive and reliable method that can be used in assessment of the diaphragmatic function and kinetics (thickness and excursion).
- There is a negative correlation between diaphragmatic function (assessed by measuring diaphragmatic thickness and excursion through U/S) and COPD severity.
- Diaphragmatic thickness is not markedly affected in mild COPD patients at low lung volumes.
- In patients with very severe COPD, the diaphragm failed to thickened adequately with changes in lung volumes, this may be due to very high FRC/TLC ratio in such patients, in addition to extremely weakened diaphragm.

REFERENCES

1. **Decramer M, De Benedetto F, Del Ponte A and Marinari S (2005):** Systemic effects of COPD. Respir Med., 99(B):3-10.
2. **Barnes PJ (2016):** Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol., 138(1): 16-27.
3. **Kim HC, Mofarrahi M and Hussain SN (2008):** Skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis., 3: 637–658.
4. **Iwasawa T, Takahashi H and Ogura (2011):** Influence of the distribution of emphysema on diaphragmatic motion in patients with chronic obstructive pulmonary disease. Jpn J Radiol., 29: 256–264.

5. **Podnar S and Harlander M (2013):** Phrenic nerve conduction studies in patients with chronic obstructive pulmonary disease. Muscle Nerve, 47: 504–509.
6. **Lopez-Navas K, Brandt S and Strutz M (2012):** Comparison of two methods to assess transdiaphragmatic pressure at different levels of work of breathing. Biomed Tech. DOI: 10.1515/bmt-2012-4124.
7. **American Thoracic Society (2002):** Statement on respiratory muscle testing. Am J Respir Crit Care Med., 166(4):518–624.
8. **Carrillo-Esper R, Pérez-Calatayud ÁA, Arch-Tirado E *et al.* (2016):** Standardization of sonographic diaphragm thickness evaluations in healthy volunteers. Respir Care, 61(7):920–4.
9. **Testa A, Soldati G and Giannuzi R (2011):** Ultrasound M-mode assessment of diaphragmatic kinetics by anterior transverse scanning in healthy subjects. Ultrasound Med Biol., 37: 44 -52.
10. **Kim BM, Park JS and Kim SW (2011):** Source apportionment of PM 10 mass and particulate carbon in the Kathmandu Valley, Nepal. Atmos Environ., 123:190–199.
11. **Vermeeren, M.A., Creutzberg, E.C and Schols (2006):** Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respir Med., 100: 1349–1355.
12. **Vesbo J, Prescott E, Almda L (2006):** Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. Am J Respir Crit Care Med., 173: 79–83.
13. **Chailleux E, Laaban JP, Veale D (2003):** Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. Chest, 123: 1460–1466.
14. **Talamo C, Montes de Oca M, Halbet R (2007):** Diagnostic labeling of chronic obstructive pulmonary disease in five Latin American cities. Chest, 131: 60–67.
15. **Kantarci F, Mihmanli I, Demirel MK *et al.* (2004):** Normal diaphragmatic motion and the effects of body composition: Determination with M-mode sonography. J Ultrasound Med., 23(2):255–60.
16. **Seok JI, Shin YK, Francis OW, Sang GK, Doo HK (2017):** Ultrasonographic findings of the normal diaphragm: thickness and contractility. Ann Clin Neurophysiol., 19(2):131-135.
17. **Kent BD, Mitchell PD and McNicholas WT (2011):** Hypoxemia in patient with COPD: causes, effects and disease progression. Int J Chronic Obstruct Pulmon Dis., 6: 199-208.
18. **Elbehairy AF, Ciavaglia CE, Webb KA *et al.* (2015):** Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. Am J Respir Crit Care Med., 191 (12): 1384–1394.
19. **Brajesh M , Apoorv S (2018):** A Comparative Study of Six Minute Walk Test (6MWT) amongst Healthy Individuals and COPD Patients. International Journal of Science and Research (IJSR), 7 (12): 791-94.
20. **Gibbons WJ, Fruchter N, Sloan S and Levy RD (2001):** Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years .Cardiopulm Rehabil., 21(2):87-93.
21. **Hatem A, Sulaiman A, Abdelrahman A (2009):** Six min walk test in a healthy adult Arab population. Respiratory Medicine, 103: 1041-1046.
22. **Chen H, Liang B, Tang Y, Zhi-bo X, Wang K, Qun Y, Feng Y (2012):** Relationship between 6-minute walk test and pulmonary function test in stable chronic obstructive pulmonary disease with different severities. Chinese Medical Journal, 125 (17):3053-3058.
23. **Ong KC, Earnest A, Lu SJ (2005):** multidimensional grading system (BODE index) as predictor of hospitalization for COPD. Chest, 128:3810–3816.
24. **Sarioglu N, Alpaydin AO and Coskun AS (2010):** Relationship between BODE index, quality of life and inflammatory cytokines in COPD patients. Multidiscip. Respir Med., 5: 84–91.
25. **Paulin LM, Diette GB, Blanc PD (2015):** Occupational exposures are associated with worse morbidity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med., 191(5): 557-65.
26. **Abd El-Aziz AA, Elwahsh R, A. Abdelaal G, Abdullah MS, Saad RA (2017):** Diaphragmatic assessment in COPD patients by different modalities. Egyptian Journal of Chest Diseases and Tuberculosis, (66): 247-250.
27. **Thimmaiah TV, Geetha MJ, Keval PJ (2016):** Evaluation of Thickness of Normal Diaphragm by B Mode Ultrasound. international Journal of Contemporary Medical Research, 9 (3): 2454-737.
28. **Jamaati HR, Shadmehr MB, Aloosh O, Radmand G, Mohajerani SA and Hashemian SM (2013):** Evaluation of plethysmography for diagnosis of postintubation tracheal stenosis. Asian Cardiovascular and Thoracic Annals, 21:181–6.