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Sonographic Assessment of Diaphragm Thickness and Its Effect on Inspiratory Muscles' Strength in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Objective: To assess diaphragm thickness and to assess its effect on inspiratory muscles' strength in patients with chronic obstructive pulmonary disease (COPD).

Methods: Case-control study was conducted on 113 male patients with COPD compared to 114 age-matched non-COPD males. Spirometric indices, maximum inspiratory pressure (MIP%), maximum expiratory pressure (MEP%), 6-min walk distance (6MWD), PaO_2, $PaCO_2$, and ultrasound measurement of diaphragm thickness were performed for all participants. The studied COPD cases were classified according to the diaphragm muscle thickness into a group with normal diaphragm muscle thickness (thickness end expiration ≥1.8 mm) and a group with diaphragm muscle thinning (thickness end expiration <1.8 mm).

Results: Thickening fraction (TF) on right side, spirometric indices, MIP%, MEP%, were significantly lower in patients with COPD than in controls. Patients with diaphragm muscle thinning represented 11.5% of patients with COPD which represent 21.7% of cases with severe-to-very severe COPD. In patients with diaphragm muscle thinning, age, smoking index, and $PaCO_2$ were significantly higher, whereas body mass index (BMI), TF bilaterally, forced expiratory volume $(FEV)_1$%, MIP%, MEP%, 6MWD, and PaO_2 were significantly lower than those with normal diaphragm muscle thickness. Additionally, TF and MIP% showed a significant negative correlation with age, smoking index, and $PaCO_2$ and a significant positive correlation with FEV_1, PaO_2, BMI, and 6MWD. By multiple logistic regression analysis, the most significant factors relevant to the diaphragm muscle thinning were forced vital capacity (FVC)%, smoking index, forced expiratory flow rate at 25-75% of vital capacity $(FEF)_{25\%-75\%}$, and FEV_1%.

Conclusion: Thinning of the diaphragm was related to COPD severity, smoking index, and older age. Reduced inspiratory muscles' strength (MIP%) was related to diaphragm thickness (TF), FEV_1/FVC ratio, smoking index, and FVC%. Assessment of diaphragm thickness in COPD patients is recommended with early implementation to pulmonary rehabilitation program.

Keywords: Diaphragm muscle thinning, inspiratory muscles' strength, inspiratory pressure, ultrasound

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease. Its management represents a challenge for clinicians, imposing a major public health problem within the 21st century (1). It is a progressively disabling disease that has a major negative impact on the quality of life including limitations on the ability to work, physical exertion, household duties, social and family activities, as well as sleeping patterns (2). Estimates show that in 2030 COPD will be the third leading cause of deaths worldwide (3).

Nowadays, it is recognized that COPD affects functions of other organs besides the lungs. Dysfunction of the respiratory muscles (RM) occurs in patients with COPD. Inspiratory muscle weakness in patients with COPD is of a major clinical relevance, and the maximum inspiratory pressure (MIP) is an independent determinant of patient's survival in severe COPD (4).

The majority of studies dealing with factors contributing to inspiratory muscle weakness in COPD have focused mainly on the diaphragm because the diaphragm is the principle muscle of inspiration (4). Inspiratory muscles' weakness in COPD is caused by hyperinflation and generalized muscle weakness that is caused by deconditioning, malnutrition, electrolyte disturbances, cardiac failure, along with systemic inflammation (5) and long-term administration of steroids (6). Additionally, in patients with COPD, the diaphragm works against an increased work load due to airflow limitation and geometrical changes in the thorax as a result of pulmonary hyperinflation (4).

In COPD, RM fibers show several degrees of cellular and subcellular structures' impairment. This structural impairment translates from the functional point of view to a loss of strength and endurance, which can result in dyspnea, impaired exercise tolerance, and an increased susceptibility to respiratory failure (7). Muscle atrophy is defined as the wasting or loss of muscle tissue, resulting from an imbalance between protein synthesis and degradation due to disease or deconditioning (4).

Data from a necropsy study indicates that ultrasound (US) measurement of diaphragm-thickness (DT) at the zone of apposition (ZOA) is as accurate as measurements performed *in vitro* with a ruler (8). In normal individuals, the DTs at functional residual capacity (FRC) show a wide range from 1.8 to 3 mm (9). The lower limit of normal DTs at end expiration or FRC is 1.5 mm, and an increase of at least 20% in DTs from FRC to total lung capacity (TLC) is considered normal (10). On the other hand, the diaphragm and other RM are able to express adaptive changes in response to the chronic hyperinflation (7). Thickening fraction (TF) [thickness end inspiration (TEI)−thickness end expiration (TEE)/TEE] or a thickening ratio (TR) (TEI−TEE) is used as an index of diaphragm efficiency as a pressure generator (9). Diaphragm TF has been proposed to be more sensitive than measurement of DTs, since the increase in DTs during inspiration is used as an indirect measurement of muscle fiber contraction (11).

Maximum inspiratory pressure and maximum expiratory pressure (MEP) are simple, convenient, and noninvasive indices of RM strength at the mouth (12). Dyspnea is the most disabling symptom in patients with COPD and could result from a decreased capacity of the RM to meet an increased mechanical load. Also, hypercapnic respiratory failure due to inspiratory muscle weakness is associated with morbidity in these patients (4). Accordingly, this study aimed to assess diaphragm thickness and its effects on inspiratory muscles' strength in patients with COPD.

METHODS

Study Design

This was an observational case-control study, conducted from January 2015 to July 2016.

Sample and Place of Study

The study was conducted on 113 patients with COPD and 114 age- and sex-matched non-COPD subjects (controls).

Selection of Subjects

1. COPD Group: Patients were recruited while they attend chest outpatient clinic for regular follow-up. COPD diagnosis was based on clinical history, physical examination, and pulmonary function tests [post-bronchodilator FEV_1/FVC<0.7(GOLD, 2014 criteria) (13) and an increase in FEV_1 of <200 mL or <12% of baseline value 20 min after four puffs of inhaled salbutamol (400 μg)]. All of them were under medications, including β2-agonists, anticholinergics, and inhaled steroids. None of them were treated by oral steroid or theophylline during the last 2 months. They were clinically stable for at least 2 months before conduction of the study.

2. Control Group: The control group consisted of a number of 114 non-COPD age- and sex-matched volunteers. All of them had no symptoms suggestive of chronic chest diseases with normal spirometric indices and arterial blood gases (ABG) parameters.

Exclusion criteria: Participants with clinical evidence of phrenic nerve injury, neuromuscular diseases, post-abdominal or thoracic surgery, muscle diseases, central bronchogenic carcinoma, severe malnutrition, or history of traumatic lesion possibly affecting diaphragm were excluded from the study.

Ethical considerations: The study was approved by the ethical review committee of our institute. Each participant participated voluntarily, gave his informed consent, and had the right to withdraw from the study at any time without affecting their rights of medical care. All data were coded to ensure confidentiality of participants.

All subjects were subjected to the following:

1. Age/year, smoking index (number of cigarettes per day×number of years), and body mass index (BMI) [weight (kg)/height^2] were recorded.
2. Spirometry was carried out on (Medisoft, Sorinnes, Belgium). The FEV_1%, FVC%, FEV_1/FVC ratio, and $FEF_{25\%-75\%}$ were measured. Spirometric indices were calculated using best out of three technically accepted performances in accordance with the recommendations of the American Thoracic Society (ATS) (14).
3. Measurement of inspiratory muscles strength: The MIP and MEP were measured using the same machine used for spirometry. The subjects were seated, wearing nose clips with a rigid plastic round mouthpiece in place during the test. The MIP was initiated from RV as it is more reproducible than FRC, while MEP was measured at the level of TLC (15). In order to avoid variability in lung volumes caused by dynamic hyperinflation; the subjects were instructed to take their time and exhale to RV and indicate when they were ready to perform another maneuver with rest periods of less than 1 min between repeated trials. Also, the subjects were encouraged to achieve maximal effort and to maintain the same volume and frequency by following the display of the maneuver on a computer screen, i.e., the end-expiratory level remained relatively constant. Data were discarded if there was an air leak around the mouthpiece or if the pressure was held for less than 1 s. Patients were also instructed to take their usual medications as scheduled on the day of testing to control for any potential drug effects on RM' function. The measurements were repeated until 3 values varying by <20% were attained (16). The best value achieved was considered in the data analysis. Patients with COPD were categorized according to condition of RM strength (MIP%) into a group with normal RM strength (MIP%>60%) and a group with reduced RM strength (MIP%<60%,) (17).
4. US measurement of diaphragmatic thickness: Diaphragmatic thickness was measured by a well-trained pulmonologist author after assessment of reliability of measurements.

A. Sonoscape A8 Medical Systems (Nanshan Shenzhen Guangdong, China) was used to examine diaphragmatic thickness. Subjects were examined in a semi-recumbent position to abolish the caudal drag of gravity on diaphragm movement. Diaphragmatic thickness was measured in the ZOA (area of the chest wall where the abdominal contents reach the lower rib cage). A high-resolution 9.5-15 MHz transducer was held perpendicular to the chest wall in the ninth intercostal space perpendicular to the ninth and tenth ribs, between the anterior and the midaxillary lines where the ZOA can be observed optimally 0.5–2 cm below the costophrenic sinus (18). In this area, the diaphragm is visualized as a structure made of three distinguishing layers: a non-echogenic central layer bounded by two echogenic layers, the peritoneum, and the diaphragmatic pleura (19). Diaphragmatic thicknesses were measured as the distance from the middle of the diaphragmatic pleura to the middle of the peritoneal membrane (Figure 1) (20).

B. Estimation of intra-observer agreement was evaluated by statistical analysis of the intra-rater reliability of measurements. Ultrasound imaging was done twice at the same anatomical position, by the same investigator 5 days apart for 15 participants as a pilot testing. Intra-rater reliability test was done by calculating intra-class correlation coefficient (ICC) using a one-way random-effect model and evaluation of absolute agreement. Confidence intervals (CI) were calculated at 95% confidence level for reliability coefficients (estimated ICC=0.90, with 95% CI, 0.75–0.98). Hence, we had an evidence of good intra-observer agreement (repeatability) of measurements between scans. The measurements of pilot test were not included in the sample of this study.

The subject was instructed to take slow deep breaths in and out. The DTs were measured during a breath-holding maneuver at the end of forced expiration (TEE) and at the end of maximal inspiration (TEI). The TF was calculated [TEI–TEE)/TEE]. The lower limit of normal TEE<1.8 mm was used as a cutoff level for diaphragm muscle thinning (9). The right hemidiaphragm is easily visualized because of the large acoustic window of the liver, while visualization of the left hemidiaphragm is more difficult because of a smaller window of the spleen. It can be facilitated by turning the patients slightly to the right side (6).

5. Exercise capacity: Exercise capacity was assessed by 6-min walking distance (6MWD), which was done according to ATS, 2002 (21). Subjects were asked to cover as much ground as possible in a period of 6 minutes but allowed to stop if there were symptoms of dyspnea; however, they were instructed to resume walking as soon as they felt able to do so. Testing was performed in a location where a rapid, appropriate response to an emergency service is available.
6. ABG: After 15-minute resting period in ambient room air, ABG was done for patients with COPD by using blood gases analyzer (Rapid Lab 248, Siemens Medical Solutions, Malvern, PA), the PaO_2 mmHg and $PaCO_2$ mmHg were recorded.

Statistical Analysis

Data were coded and statistically analyzed by using the Statistical Package for the Social Sciences Statistics for Windows, version 17.0 (SPSS Inc.; Chicago, IL, USA). Data were expressed as mean±SD for quantitative variables. The studied patients with COPD were categorized into two groups based on their TEE into a group with normal diaphragm muscle thickness (≥1.8 mm) and a group with diaphragm

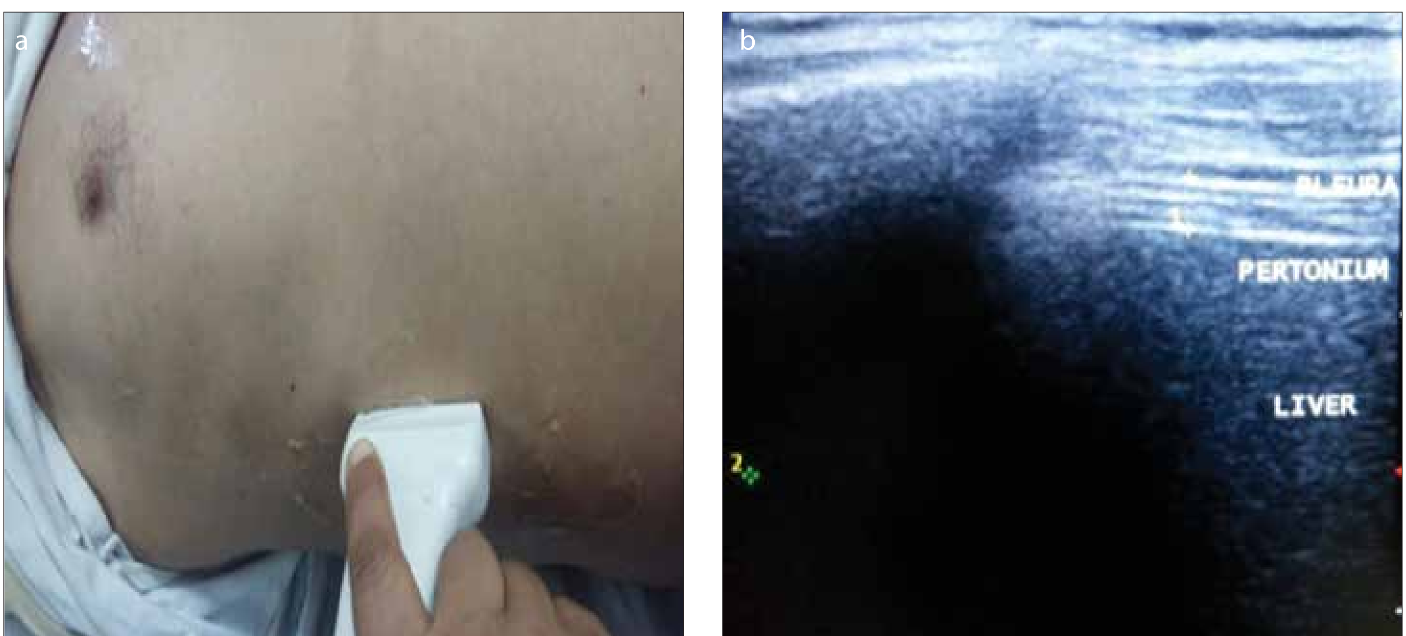

Figure 1. a, b. US measurement of diaphragmatic thickness. (a) First figure demonstrated that subjects were examined in a semi-recumbent position. A high-resolution 9.5–15 MHz transducer was held perpendicular to the chest wall in the ninth intercostal space perpendicular to the ninth and tenth ribs, between the anterior and the midaxillary lines where the ZOA can be observed optimally 0.5–2 cm below the costophrenic sinus. In this area, the diaphragm is visualized as a structure made of three distinguishing layers: a non-echogenic central layer bounded by two echogenic layers, the peritoneum, and the diaphragmatic pleura. (b) Diaphragmatic thickness was measured in the ZOA (area of the chest wall where the abdominal contents reach the lower rib cage). Diaphragmatic thicknesses were measured as the distance from the diaphragmatic pleura to the peritoneal membrane

US: Ultrasonography; ZOA: zone of apposition muscle thinning (<1.8 mm), also patients with COPD were categorized into two groups according to the level of MIP%. Shapiro-Wilk test was used for testing the normality of the studied variables and the Student's *t* test was used for comparisons between the studied groups. Pearson correlation test was used to study the relationship between the related quantitative variables. Both the direction and the strength of association were determined by the value of correlation coefficient (r) and the p value. Multiple logistic regression analysis was used to identify the most relevant risk factors affecting thickness of the diaphragm and MIP% among patients with COPD. The strength of relevance between the risk factors and the outcome was determined according to the value of the Beta regression coefficient (B) and significance of the Wald Chi-square test and the Odds Ratio (OR) (Exp (B)) for each variable. We analyzed the intra-observer reliability by calculating ICC with 95% CI. Agreement levels were classified as poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) and excellent (>0.80) (22). Statistical significance was considered at p value ≤0.05 (with a confidence limit at 95%). Results were presented by tables and figures.

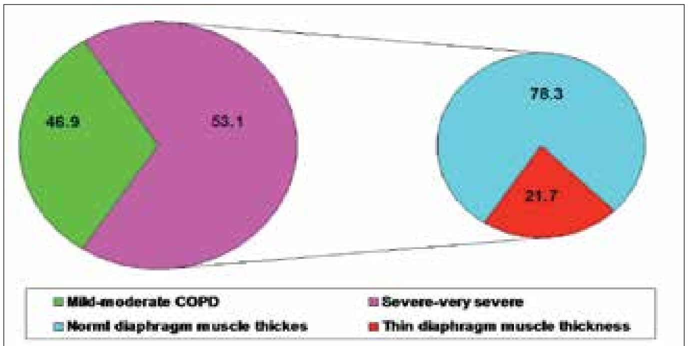

Figure 2. Distribution of COPD patients according to severity of airflow limitation and diaphragm muscle thinning. This figure demonstrates that 46.9% of patients with COPD had mild-to-moderate COPD, while 53.1% had severe to-very severe COPD. Additionally, 21.7% among patients with severe-to-very severe COPD had diaphragm muscle thinning

COPD: Chronic obstructive pulmonary disease

RESULTS

This study was conducted on 113 male patients with COPD and 114 age- and sex-matched healthy subjects. The studied patients with COPD were categorized into one group with reduced MIP% (79.6 %) and other group with normal MIP% (20.4%). The smoking index and $PaCO_2$ were significantly higher, while right TF, spirometric indices, MIP%, MEP%, 6MWD, and PaO_2 were significantly lower in patients with COPD than in controls. The TEE and TEI bilaterally were non-significantly different between both the groups (Table 1).

Figure 2 demonstrates that 46.9% of patients with COPD had mild-to-moderate COPD versus 53.1 % who had severe to-very severe COPD, among them 21.7% had diaphragm muscle thinning.

Table 2 demonstrates that age, smoking index, and $PaCO_2$ were significantly higher, while right and left TF, FEV_1/FVC ratio, FEV_1%, MIP%, MEP%, 6MWD, and PaO_2 were significantly lower in patients with COPD with diaphragm muscle thinning than in those with normal diaphragm muscle thickness. Table 3 and Figures 3a–c and 4 demonstrate that the right TF, left TF, and MIP% were negatively correlated with age, smoking index, and $PaCO_2$. The right TF, left TF, and MIP% were positively correlated with FEV_1, PaO_2, BMI, and 6MWD among COPD with diaphragm muscle thinning.

Multiple logistic regression analysis (Table 4) revealed that the most significant risk factors relevant to the diaphragm muscle thinning among patients with COPD were FVC% (B= −0.17, OR=1.18) followed by smoking index (B=0.003, OR=1.00), $FEF_{25\%-75\%}$ (B=−0.16, OR=0.85) and FEV_1% (B=0.19, OR=0.82).Moreover, FEV_1/FVC ratio, age, and BMI were insignificantly relevant to diaphragm muscle thinning. Multiple logistic regression analysis (Table 5) revealed that the most significant risk factors relevant to the reduced MIP among patients with COPD were right TF (B=0.21, OR=1.233) followed by FEV_1/FVC ratio (B=0.085, OR=1.089), smoking index (B=0.002, OR=1.00), and FVC % (B=−0.091, OR=0.913).

DISCUSSION

Diaphragm strength is defined as the capacity of the diaphragmatic muscle to generate force under isometric condition (23), while en-

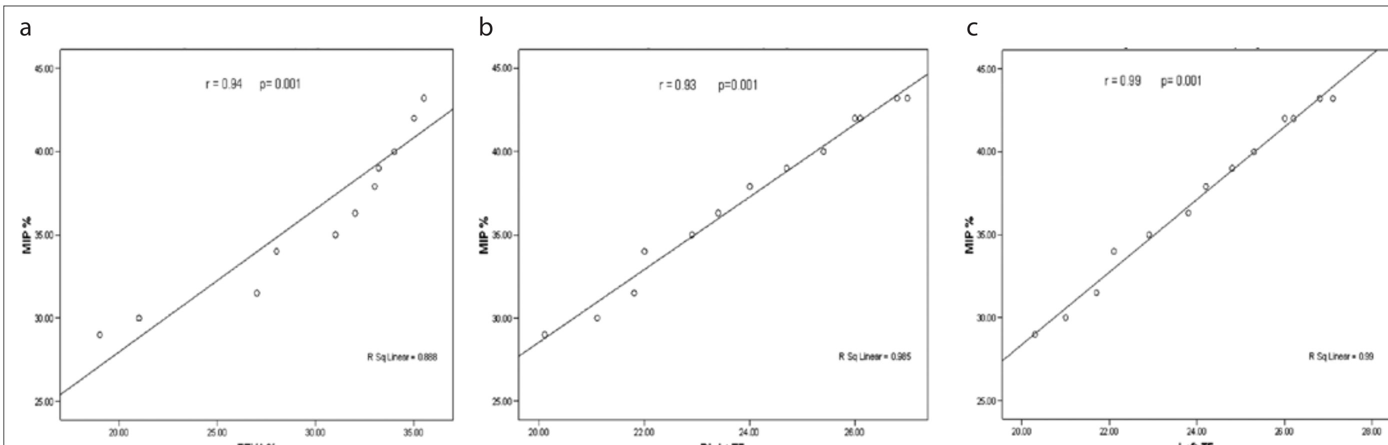

Figure 3. a-c. Scatter plot of MIP with FEV_1% (a), right thickness fraction (b), and left thickness fraction (c) among COPD group with thinning of diaphragm muscle. This figure demonstrates that the FEV_1, right thickness fraction, and left thickness fraction were positively correlated with MIP% among COPD group with thinning of diaphragm muscle

COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in first second; MIP: maximum inspiratory pressure

Table 1. Comparison between COPD group and control group regarding all the studied parameters

Groups Items	COPD group (n=113) Mean±SD	Control group (n=114) Mean±SD	Significance test t test	p
Age, y	62.7±8.8	61.6±5.7	1.2	0.22
BMI, kg/m^2	28.9±5.2	29.3±3.1	0.7	0.49
Smoking index	968.5±399.3	245.7±104.5	18.7	0.001*
FEV_1/FVC ratio	57.9±14.5	92.2±10.8	20.1	0.001*
FEV_1%	47.7±19.1	81.9±8.4	17.5	0.001*
FVC%	61.9±18.8	92.7±10.6	15.2	0.001*
$FEF_{25\%–75\%}$	34.8±17.3	72.1±7.1	21.2	0.001*
PaO_2 mmHg	68.6±11.1	79.1±7.2	8.4	0.001*
$PaCO_2$ mmHg	42.3±8.5	39.8±3.1	2.9	0.003*
MIP%	51.1±18.9	78.8±12.6	12.9	0.001*
MEP%	58.2±19.4	73.6±10.9	11.2	0.001*
6MWD, m	248.8±68.4	384.3±46.4	17.4	0.001*
Right TEE, mm	2.9±0.9	2.9±0.4	0.4	0.72
Right TEI, mm	3.8±0.9	3.7±0.5	1.3	0.16
Right TF%	29.5±4.1	31.8±4.6	3.9	0.001*
Left TEE, mm	2.8±0.7	2.9±0.4	0.8	0.41
Left TEI, mm	3.8±0.9	4.1±0.9	1.5	0.13
Left TF%	33.3±6.6	34.1±9.9	0.7	0.48

*Significant p-value
Smoking index and $PaCO_2$ were significantly higher, while right TF, spirometric indices, MIP%, MEP%, 6MWD, and PaO_2 were significantly lower in COPD group compared to control group. Right and left TEE and TEI as well as left TF were not significantly different between both groups
BMI: Body mass index; COPD: chronic obstructive pulmonary disease; $FEF_{25-75\%}$: forced expiratory flow rate at 25-75% of vital capacity; FEV_1/FVC ratio: forced expiratory volume in first second/forced vital capacity; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; $PaCO_2$: partial pressures of carbon dioxide; PaO_2: partial pressures of oxygen; SD: standard deviation; TEE: thickness end expiration; TEI: thickness end inspiration; TF: thickening fraction; 6MWD: 6-min walk distance

Table 2. Comparison between patients with COPD with normal diaphragm muscle thickness and patients with COPD with diaphragm muscle thinning regarding all the studied parameters

Groups Items	COPD with normal diaphragm muscle thickness n=100 (88.5%) Mean±SD	COPD with diaphragm muscle thinning n =13 (11.5%) Mean±SD	Significance test t test	p
Age, y	62.0±8.7	68.5±7.3	2.5	0.01*
BMI, kg/m$_2$	29.4±5.2	24.4±2.1	3.44	0.001*
Smoking index	871.5±305.2	1714.3±197.8	9.6	0.001*
FEV_1/FVC ratio	58.7±14.6	50.2±11.9	2.06	0.04*
FEV_1%	49.9±19.2	30.7±5.45	3.58	0.001*
FVC%	61.5±19.2	65.4±15.5	0.69	0.49
FEF25%–75%	70.3±10.4	29.4±16.2	1.20	0.23
PaO_2 mmHg	70.3±10.4	55.2±5.4	5.13	0.001*
$PaCO_2$ mmHg	40.9±7.6	53.3±7.6	5.53	0.001*
MIP%	52.9±19.3	37.2±4.9	2.91	0.004*
MEP%	59.5±20.1	48.6±7.3	1.91	0.06
6MWD, m	261.2±62.7	154.2±15.2	6.11	0.001*
Right TEE, mm	3.1±0.8	1.8±0.03	5.81	0.001*
Right TEI, mm	4.0±0.8	2.5±0.2	6.76	0.001*
Right TF%	32.8±3.7	23.9±2.3	8.40	0.001*
Left TEE, mm	2.9±0.7	1.7±0.03	6.33	0.001*
Left TEI, mm	3.9±0.9	2.8±0.2	4.68	0.001*
Left TF%	34.6±5.9	24.1±2.3	6.34	0.001*

*Significant p value
Age, smoking index, and $PaCO_2$ were significantly higher, while BMI, right and left TF, FEV_1/FVC ratio, FEV_1%, MIP%, MEP%, 6MWD, and PaO_2 were significantly lower in patients with COPD with diaphragm muscle thinning compared to COPD with normal diaphragm muscle thickness
BMI: Body mass index; COPD: chronic obstructive pulmonary disease; $FEF_{25-75\%}$: forced expiratory flow rate at 25-75% of vital capacity; FEV_1/FVC ratio: forced expiratory volume in first second/forced vital capacity; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; $PaCO_2$: partial pressures of carbon dioxide; PaO_2: partial pressures of oxygen; SD: standard deviation; TEE: thickness end expiration; TEI: thickness end inspiration; TF: thickening fraction; 6MWD: 6-min walk distance

durance is the capacity to maintain a certain force over time. The loss in either strength or endurance results in diaphragm weakness and impaired performance (4).

This study revealed that right TF was significantly reduced in COPD group, while other parameters of diaphragm muscle thickness (TEE and TEI bilaterally and left TF) showed no significant difference between patients with COPD and controls. In accordance with these results, Baria et al. (24) reported a non-significant difference in diaphragm thickness between patients with COPD and healthy subjects; however, the left thickening ratio (TR) was statistically increased in COPD subgroup with air trapping compared with both COPD group and control group. Therefore, they concluded that diaphragm dysfunction, in patients with COPD, may reflect mechanical impairment secondary to lung hyperinflation, rather than physiologic alteration of contractility.

Results of the current study showed that diaphragm muscle thinning with reduction of diaphragm contractility (TF) was detected in 11.5% of patients with COPD which constitute 21.7% of those with severe-to-very severe COPD. In the same context, previous studies reported reduced diaphragm fiber cross-sectional area in either type-I and type-II fibers in patients with severe COPD (25) or predominantly in type-I fibers (26). Meanwhile, the reduction in fiber cross-sectional area has not been found in mild or moderate patients with COPD as mentioned by other authors (27, 28). However, other studies reported a contractile protein loss of diaphragm in patients with mild-to-moderate COPD (28-30). Also, Ottenheijm et al. (4) reported that diaphragm fiber atrophy is a consistent finding in patients with severe COPD, which results in reduced force production.

The main findings of this study is that the diaphragm contractility (TF) bilaterally was significantly reduced in COPD with diaphragm muscle

Table 3. Pearson correlation of right TF, left TF, and MIP with the related factors among patients with COPD with thinning of diaphragm

	Right TF		Left TF		MIP%	
Item	r	p	r	p	r	p
Age, y	–0.97**	0.001	–0.98**	0.001	–0.98**	0.001
BMI, kg/m^2	0.95**	0.001	0.95**	0.001	0.93**	0.001
Smoking index	–0.98**	0.001	–0.97**	0.001	–0.97**	0.001
FEV_1//FVC ratio	0.31	0.30	0.29	0.32	0.30	0.31
FEV_1%	0.92**	0.001	0.93**	0.001	0.94**	0.001
FVC%	0.043	0.88	0.03	0.89	0.05	0.86
$FEF_{25\%–75\%}$	0.21	0.48	0.20	0.50	0.22	0.46
PaO_2 mmHg	0.85**	0.001	0.85**	0.001	0.86**	0.001
$PaCO_2$ mmHg	–0.92**	0.001	–0.97**	0.001	–0.97**	0.001
MIP%	0.93**	0.001	0.99**	0.001	---	---
MEP%	0.98**	0.001	0.98**	0.001	0.97**	0.001
6MWD, m	0.95**	0.001	0.95**	0.001	0.95**	0.001
Left TF%	0.99**	0.001	---	---	---	

**Significant r value

Right TF, left TF, and MIP% were negatively correlated with age, smoking index, and $PaCO_2$. The right TF, left TF, and MIP% were positively correlated with FEV_1%, PaO_2, BMI, and 6MWD among patients with COPD with thin DTs

BMI: Body mass index; COPD: chronic obstructive pulmonary disease; $FEF_{25-75\%}$: forced expiratory flow rate at 25-75% of vital capacity; FEV_1/FVC ratio: forced expiratory volume in first second/forced vital capacity ratio; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; $PaCO_2$: partial pressures of carbon dioxide; PaO_2: partial pressures of oxygen; TF: thickening fraction; 6MWD: 6-min walk distance

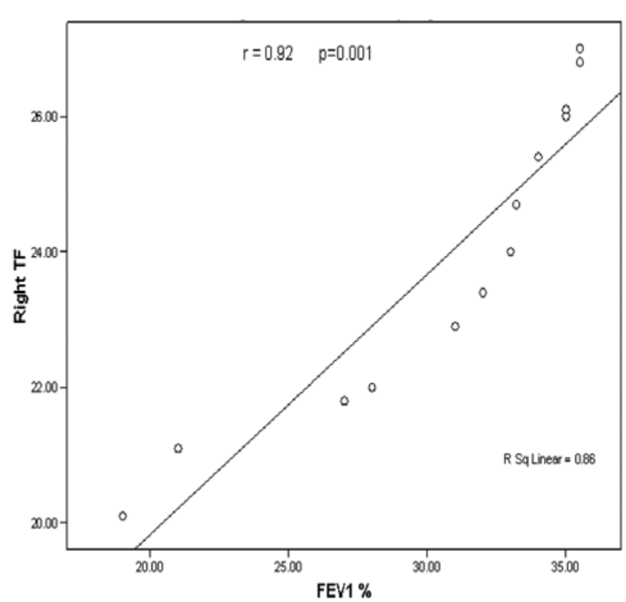

Figure 4. Scatter plot of FEV_1% with right thickness fraction among COPD group with thinning of diaphragm muscle. This figure shows that FEV_1% was positively correlated with right TF among patients COPD with thinning of diaphragm muscle
COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume; TF: thickening fraction

Table 4. Multiple logistic regression of the most relevant factors to diaphragm muscle thinning among patients with COPD

				Significance	Exp	95% CI for Exp (B)	
Item	B	S.E.	Wald		(B)	Lower	Upper
FVC%	-0.17	0.07	6.47	0.01*	1.18	1.03	1.34
Smoking index	0.003	0.001	7.38	0.007*	1.00	1.00	1.00
$FEF_{25\%–75\%}$	-0.16	0.08	4.03	0.04*	0.85	0.73	0.99
FEV_1%	-0.19	0.08	6.19	0.01*	0.82	0.70	0.96
FEV_1/FVC ratio	0.08	0.06	1.88	0.17	1.08	0.96	1.22
Age, y	-0.03	0.06	0.24	0.62	0.96	0.85	1.09
BMI	-0.18	0.16	1.22	0.27	0.84	0.61	1.14
Constant	-2.69	6.56	0.17	0.68	0.07		

*Significant p value

Regression coefficient (B), the Wald statistic, and the OR (Exp (B)) for each variable. It revealed that the most significant factors relevant to the diaphragm muscle thinning among patients with COPD were FVC% (B=–0.17, OR=1.18) followed by smoking index (B=0.003, OR=1.00), $FEF_{25\%–75\%}$ (B=–0.16, OR=0.85) and FEV_1% (B=0.19, OR=0.82). Moreover, FEV_1/FVC ratio, age, and BMI were insignificantly relevant to diaphragm muscle thinning

BMI: Body mass index; COPD: chronic obstructive pulmonary disease; $FEF_{25\%–75\%}$: forced expiratory flow; FEV_1/FVC: forced expiratory volume/forced vital capacity; SE: standard error

Table 5. Multiple logistic regression of risk factors for reduced MIP among patients with COPD

				Significance	Exp	95% CI for Exp (B)	
Items	B	S.E.	Wald		(B)	Lower	Upper
Right TF	0.210	0.078	7.274	0.007*	1.233	1.059	1.436
FEV_1/FVC ratio	0.085	0.024	12.750	0.000*	1.089	1.039	1.141
Smoking index	0.002	0.001	9.151	0.002*	1.002	1.001	1.004
FVC%	-0.091	0.023	16.350	0.000*	0.913	0.873	0.954
Constant	-4.978	2.995	2.762	.097	.007		

*Significant p value

Regression coefficient (B), the Wald statistic, and the OR (Exp (B)) for each variable. It revealed that the most significant risk factors relevant to the reduced MIP among patients with COPD were right TF (B=0.21, OR=1.233) followed by FEV_1/FVC ratio (B=0.085, OR=1.089), smoking index (B=0.002, OR=1.00), and FVC % (B=-0.091, OR=0.913)

FEV_1/FVC ratio: forced expiratory volume in first second / forced vital capacity ratio; SE: standard error

thinning compared to patients with COPD with normal diaphragm muscle thickness (Table 2). Furthermore, in patients with diaphragm muscle thinning, the TF showed strong positive correlation with inspiratory muscles' strength (MIP%) and FEV_1% (Table 3), with the most significant factors relevant to the diaphragm muscle thinning being FVC%, smoking index, $FEF_{25\%–75\%}$, and FEV_1% (Table 4). These findings point to that in patients with severe-to-very severe COPD, the diaphragm is still the main determinant of inspiratory muscles' strength, taking into consideration that the contribution of other inspiratory muscles to MIP was not assessed in this study. Other studies demonstrated that patients with severe COPD generate less MIP than patients without COPD (31, 32). Similarly, TR was positively correlated with MIP in normal subjects (10) and in patients with COPD (18, 32, 33). In the same context, Orrey et al. (23) found a moderate positive correlation between diaphragm thickness and diaphragm strength. Also, Topeli et al. (34) reported normal diaphragm structure function, and normal respiratory drive was detected in patients with COPD. The strong positive correlation between diaphragm contractility (TF) and COPD severity (FEV_1%) detected in this study signifies that with progression of COPD, increased airflow obstruction caused dynamic air trapping; consequently, hyperinflation-induced diaphragm shortening developed, which places the diaphragm on a suboptimal position on its force-length relationship that limits its ability to contract, which eventually leads to diaphragm muscle thinning. In the same context, Smargiassi et al. (6) reported that the diaphragm thickness and TR were related to FEV_1 and FVC with no significant difference in diaphragm thickness between GOLD A, B, C, D groups. Another study reported a positive correlation between diaphragm thickness and FEV_1% in mild COPD group but not in moderate and severe COPD groups (8).

This study revealed that among patients with COPD with diaphragm muscle thinning, TF bilaterally and MIP% were positively correlated with MEP% (Table 3) with the most significant factors relevant to the reduced MIP% among patients with COPD being right TF, FEV_1/FVC ratio, smoking index, and FVC % (Table 5), which suggests that in patients with COPD, there were parallel reductions of inspiratory and expiratory pressures. Since it is well known that the muscles of expiration are not at a mechanical disadvantage, these findings imply that patients with COPD have generalized RM weakness. In accordance with these results, previous studies reported good positive correlation between MIP% and MEP% in patients with COPD (31, 35).

Additionally, results of this study showed that patients with COPD with diaphragm muscle thinning were older in age and have significantly higher smoking index, $PaCO_2$, with significantly lower BMI, PaO_2, and 6MWD compared to patients with COPD with normal diaphragm muscle thickness. These findings specify that the aging process, BMI, and smoking are contributing factors to diaphragm thinning with reduction in its contractility, which subsequently leads to respiratory failure and worsening of function exercise capacity. Similarly, other studies reported that diaphragm thickness was related to smoking history (10) and BMI (6). However, Cimsit et al. (8) reported that diaphragm thickness was not related to BMI.

In this study, the underlying mechanism for diaphragm muscle thinning was not assessed. Therefore, we cannot conclude whether malnutrition, smoking, steroids use, or any other COPD-related factors contribute to diaphragm muscle thinning, which leads to reduction of its contractility or the hyperinflation, put the diaphragm at mechanical disadvantages with reduction of its contractility, and subsequent underuse thinning of diaphragm muscle.

CONCLUSION

Diaphragm muscle thinning was detected in 11.5% of patients with COPD; they have higher mean age, severe airflow limitation, and smoking index, with lower BMI and exercise capacity. Diaphragm muscle thinning has negative impact on inspiratory muscles' strength. Accordingly, assessment of diaphragm thickness in patients with COPD is highly recommended for the early detection of diaphragm dysfunction with early implementation and adherence to pulmonary rehabilitation program to improve respiratory muscles' function.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Faculty of Medicine Al-Azhar University.

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

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