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Research Article

The Importance of Measuring the Fraction of Diaphragmatic Thickening in Patients with COPD

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Keywords: Pulmonary disease; Chronic obstructive; Diaphragm thickening fraction; Spirometry; Dyspnea; Ultrasound; GOLD classification 2023

Abstract

In addition to affecting the respiratory system, chronic obstructive pulmonary disease also decreases muscle mass. The respiratory muscles weaken, which impairs ventilation and exercise tolerance. According to recent studies, ultrasonography is a dependable and user-friendly method for determining the diaphragm thickening fraction (TFdi) in patients with COPD.

Objective: Evaluate the diaphragm thickening fraction by ultrasound in patients with COPD and correlate with different clinical, ventilatory variables, and the six-minute walking test.

Méthods: We conducted a prospective, observational study from 2021 to 2024. A total of Sixty-one consecutive patients with spirometry-confirmed stable COPD were included after obtaining informed written consent. Demographic and clinical data, spirometric values, the mMRC dyspnea score, the number of exacerbations, the COPD Assessment test (CAT), GOLD classification 2023, and the diaphragm thickening fraction (TFdi) were collected for analysis.

This is a prospective study conducted at Constantine Regional Military University Hospital.

Results: The mean of diaphragm thickening fraction, evaluated by ultrasound (Tfdi), in our patients with COPD was 48,9 ± 21.1%, The average BMI is 24.12 4.83 kg/m 2, with extreme values ranging from 14.6 to 36.9 kg/m 2, a positive correlation has been reported between Tfdi and the BMI (p = 0,003) a negative correlation has been reported between Tfdi and the dyspné MMRC, in our study, no objective correlation was found between TFdi and blood gas in our cohort, the average of FVC pré = 3,52 (L), FEV1 pré (L/s)) 1,91, FEV1/FVC pré (%) = 53,57, a correlation between the Tfdi and spirometric data (FVC; FEV1; FEV1/FVC) was objectified, finally our study has shown that the more Tfdi increases, the distance patients travel increases (p = 0,001).

Conclusion: In patients with COPD, diaphragm thickening fraction (TFdi) appears to be associated with airway obstruction and BMI, 6-minute walking test as well as blood gas and perception of dyspnea.

Introduction

COPD is a major public health problem and is a leading cause of chronic morbidity and mortality worldwide. The prevalence of COPD is difficult to assess because it requires patient cohorts representative of the entire population using spirometric measurements [1].

An estimated 384 million people had COPD in 2010 and the global prevalence is estimated at 11.7% (8.4% - 15.0%) in 2015 [2].

According to the BOLD study, Chronic Obstructive Pulmonary Disease (COPD) is a significant public health issue and a primary cause of morbidity and mortality globally: COPD affects 10.1% of those over 40, and it is thought to cause three

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million deaths annually. The BREATHE study estimates that the prevalence of COPD in Algeria is 25% among smokers and 4% in the general population [3,4].

The diaphragm plays a crucial role not only in breathing, but also in maintaining posture, defecation, and delivery. Diaphragmatic contraction generates two important and closely related actions: shortening and force production [5].

Diaphragmatic dysfunction is a typical symptom of Chronic Obstructive Pulmonary Disease (COPD). The primary and most ancient reason for Diaphragmatic dysfunction is a mechanical issue in COPD patients brought on by excessive lung emphysema [6]. COPD significantly impacts the diaphragm through several factors such as aging, sedentary lifestyle, oxidative stress, inflammation, hypoxemia, and energy imbalance [7].

During COPD, the diaphragm muscle fibers undergo several changes:

- 30% decrease in heavy chain myosin [8].
- Reduction of 40-60% in cross-sectional area, affecting all types of fibers [9].
- Decreased diaphragm contractility [10].
- Change of fiber type composition through a process known as "fiber change" or "transformation" from type II to type I [9,11].
- Increase in capillary count by fiber type compared to healthy control subjects and increase in capillary contact with each fiber type [11].
- Increase in the ratio of oxidative enzymes/glycolytic enzymes [11].

Currently, techniques such as X-rays, phrenic nerve stimulation, trans-diaphragmatic pressure measurement, and electromyography are used to assess the function of the diaphragm [5,12,13]. However, there are limitations to these methods, including radiation exposure, invasiveness, and technical difficulties. Ultrasound, on the other hand, has many advantages: it is fast, accurate, simple, non-invasive, easy to perform, reproducible, inexpensive, radiation-free, and achievable in a patient bed without mobilization [14,15]. Ultrasound is used to assess the function of the diaphragm by measuring its thickness, thickening fraction (Tfdi) and excursion (Exdi).

During inspiration, the muscle fibers contract, increasing diaphragm thickness. This rate of increase, known as the thickening fraction, can be expressed as a percentage and provides an indirect approximation of the contractile capacity of the diaphragm [16]. Ultrasound can assess the activity, function, and force reserve of the diaphragm [17], The mean thickening fraction in healthy subjects described in the literature is 61.96% according to [18], is 60.2% according to [19], An (Tfdi) of less than 20% in spontaneous ventilation would indicate diaphragmatic dysfunction [20].

Methods

Study design and participants

This is a prospective descriptive observational study conducted in the HMRUC's Department of Pneumology, 61 patients participated in the study. According to the Global Initiative criteria for chronic obstructive pulmonary disease (GOLD). Inclusion criteria: All patients with COPD, over 40 years of age, in stable condition. Criteria for non-inclusion: Restrictive respiratory pathology, Progressive cardiovascular disease, Recent surgery (less than 3 months), All patients who did not pass all the tests in the study protocol were excluded.

A cross-sectional study design was used. All participants underwent ultrasonographic evaluation, nocturnal oximetry, and other measurements (i.e. pulmonary function). This study was approved by the medical ethics committee of Constantine Regional Military University Hospital, The objective and content of the study were explained verbally as well as in written documents to the participants. Written consent was obtained after the subjects were informed that they could decide whether to participate based on their own free will and that their privacy would be reasonably protected.

Ultrasound measurements of diaphragm

The ultrasound examination was performed by a single specialized and trained professional using a TOSHIBA device, model SSA-370^{a} Power Vision 6.000.

The right heme diaphragm was examined in B and M mode ultrasound, as it is more easily visualized due to the large acoustic window of the liver. However, the visualization of the left diaphragm is more complex due to the narrower acoustic window of the spleen.

We measured the thickness of the diaphragm (Tfdi) in the zone of apposition using B-mode ultrasound imaging. In the supine position, an 18-5 MHz linear transducer was placed on the chest wall in the eighth or ninth right intercostal space between the anterior-axillary and mid-axillary lines [21,22] (Figure 1). The subject was instructed to take slow deep breaths in and out.

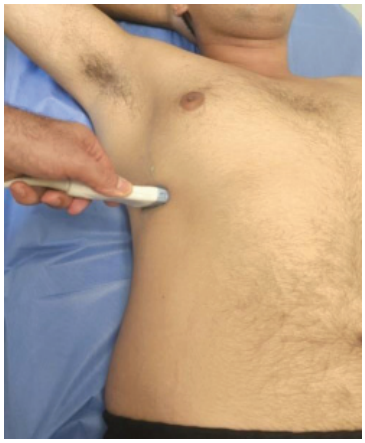

Figure 1: Ultrasound measurement of diaphragm thickness.

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The measure during a breath-holding maneuver at the end of forced expiration (TEE) and at the end of maximal inspiration (TEI). The TFdi was calculated [TEI-TEE)/TEE] (Figures 2,3).

Other measurements

An arterial blood sample was obtained by puncture of the radial artery for blood gas analysis, namely arterial oxygen pressure (PaO_2) and arterial carbon dioxide pressure ($PaCO_2$).

Dyspnoea was assessed using the modified Medical Research Council (MMRC) dyspnoea scale.

Degree 0: patient with dyspnea during intense exercise.

Degree 1: dyspnea when walking fast on flat ground or climbing a slope light.

Degree 2: walks slower than people of his age on flat ground, or must Stop for breath when walking at your own pace on flat ground.

Degree 3: must stop to breathe after a walk of about 90 meters.

Degree 4: too breathless to leave home, or dyspnea when dressing.

The six-minute walking test TM6: The walking test is a field test that is characterized by its simplicity, reliability, validity, performance, security, reduced cost, and reproducibility.

This is a comprehensive endurance test, with a moderately higher intensity than normal for everyday life activities. It measures the ability to adapt to effort in people with COPD [23].

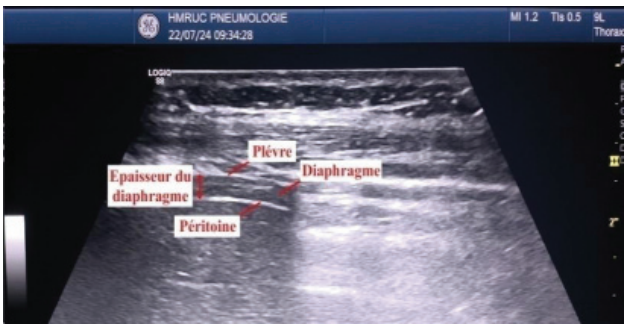

Figure 2: Measurement of the thickening of the diaphragm at the end of inspiration.

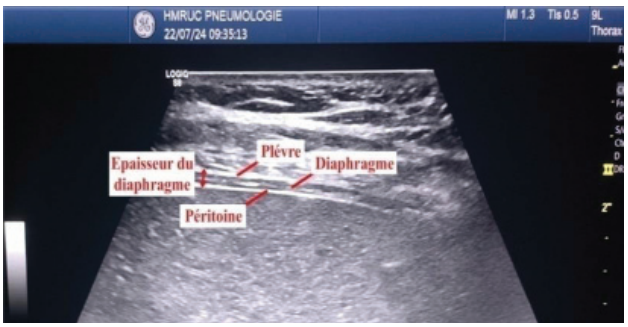

Figure 3: Measurement of the thickening of the diaphragm at the end of expiration.

Performed according to the recommendations of the American Thoracic Society/European Respiratory Society statements [24].

Statistics analysis

Data was captured and analyzed using IBM SPSS 24.

Many procedures of control at the time of entry have been established to avoid errors as much as possible.

We have implemented the following statistical methods:

- Frequencies and percentages for qualitative data.
- The means, standard deviation, maximum, and minimum for quantitative data.
- The normality of quantitative variables was investigated by the Shapiro-Wilk test.
- Comparisons of summer averages performed by the Student t-test or ANOVA test according to the number of modalities of the variable.
- Comparisons between categorical or nominal variables were made by the Chi2 test or, where appropriate, by the exact Fisher test.
- The study of relationships between quantitative variables was analyzed by the Pearson or Spearman correlation coefficient as a function of the statistical distribution of variables.

The statistical tests used were considered significant when p 0.05 (degree of significance).

Results

The majority of patients included in the study are in both age groups 60 to 70 and 70 to 79, representing 73.8% of the total population (Figure 4), the population in our study is almost exclusively male 1 female/60 male. Sex-ratio = 0.017, the average BMI is 24.12 4.83 kg/m 2, with extreme values ranging from 14.6 to 36.9 kg/m 2, a positive correlation has been reported between Tfdi and the BMI (p = 0,003)

The mean of diaphragm thickening fraction, evaluated by ultrasound (Tfdi), in our patients with COPD was 48, 9 ± 21.1%.

Three groups of patients were identified according to smoking status:

- Ex-smokers: They represent the majority of our cohort with 73.8% of patients (n = 45).
- Active smokers: 22.9% of patients are active smokers (n = 14).
- Non-smokers: Only 3.3% of patients have never smoked (n = 2) (Figure 5), the majority of our patients were classified as grade 1 and grade 2 according to MMRC (Figure 6), a negative correlation has been reported between Tfdi and the dyspné MMRC (p < 0,001) (Table 1).

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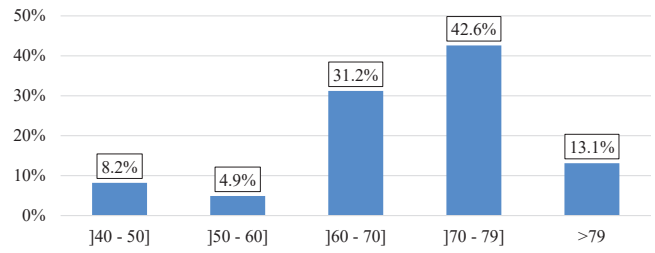

Figure 4: Distribution of patients by age group.

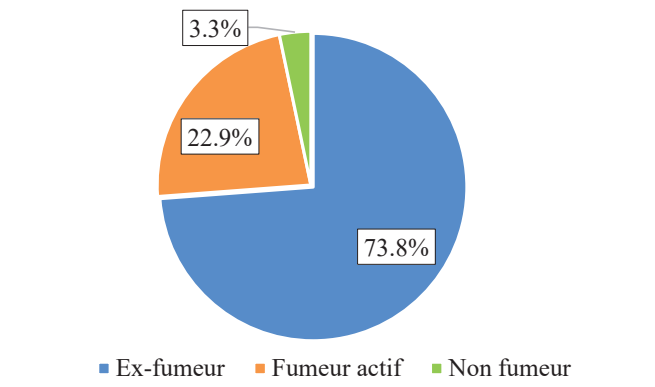

Figure 5: Distribution of patients by smoking status.

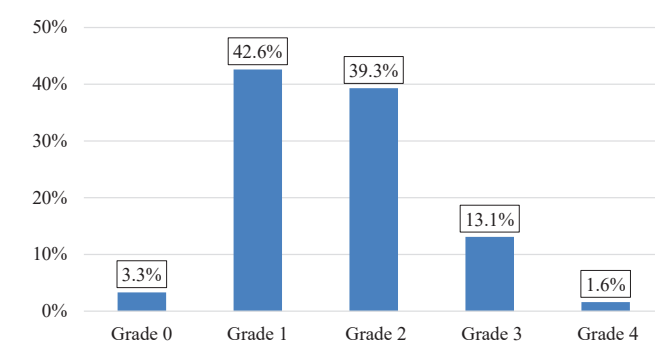

Figure 6: Patient distribution according to mMRCscale.

The average of $PaCO_2$ is 36,57 (mmHg) (Table 2).

- 62.3% of the patients in our series have a pH between 7.38 and 7.42, 34.4% have a pH > 7.42, and 3.3% have a pH < 7.38.
- 45.9% of the patients in our series have a PaO_2 between 75 and 100 mmHg, 52.5% have a PaO_2 < 75 mmHg.
- 85.24% of the patients in our series have a $PaCO_2$ between 35 and 45 mmHg, 11.47% have a $PaCO_2$ > 45 mmHg and 3.2% have a $PaCO_2$ < 35 mmHg.
- 83.6% of patients in our series have a SaO_2 between 94 and 100%, 14.8% have a SaO_2 < 94% in our study, no objective correlation was found between TFdi and blood gas (Table 3) in our cohort, the average of FVC pré = 3,52 (L), FEV1 pré (L/s)) 1,91, FEV1/FVC pré (%) = 53,57 (Table 4), In our study a correlation between the Tfdi and spirometric data (FVC; FEV1; FEV1/FVC) was objectified (Table 5). The average distance traveled in this test was 470 129.37 m, the study has shown that the more Tfdi increases, the distance patients travel increases (p = 0,001) (Figure 7) in our cohort, the average of CAT is 14,25, and a negative correlation has been reported between Tfdi and the CAT Coefficient PEARSON = - 0,717 p = 0,001 (Figure 8).

Table 1: Correlation between TFdi and dyspnea.

	TFdi	
	Pearson correlation	*p* value
Evaluation of dyspnea according to mMRC	-0,591	<0,001*
Evaluation of dyspnea according to Sadoul	-0,555	<0,001*

*: The correlation is significant; TFdi: Thickening fraction of diaphragm

Table 2: Gas characteristics of the population studied.

parameters	average	Écart-type
PH	7,41	0,03
PaO_2(mmHg)	73,20	9,08
$PaCO_2$(mmHg)	36,57	4,62
SaO_2(%)	95,25	2,14

Table 3: Correlation between TFdi and blood gas.

	TFdi	
	Pearson correlation	*p* value
PaO_2 (mmHg)	0,189	0,147
$PaCO_2$ (mmHg)	-0,133	0,310
PH	-0,82	0,529

Table 4: Spirometric characteristics of the studied population.

	average	Standard dedededeviationDeviation
FVC		
FVC pré (L)	3,52	0,92
FVC post (L)	3,63	0,90
FEV1		
FEV1 pré (L/s)	1,91	0,69
FEV1 post (L/s)	2,00	0,71
FEV1/FVC (%)		
FEV1/FVC pré (%)	53,57	10,56
FEV1/FVC post (%)	54,74	11,73
FEV1 post – FEV1 pré (L/s)	110	90
(FEV1 post – FEV1 pré) / FEV1 pré (%)	6,7	5

Table 5: Correlation between EXdi and spirometric data.

	TFdi	
	Pearson correlation	*p* value
FVC	0,256	0,047
FEV1	0,418	0,001
FEV1/FVC	0,448	0,000

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Finally, Patients in group E according to GOLD 2023, constitute more than half of our cohort, representing 54.1% of cases (Figure 9), a negative correlation has been reported between Tfdi and the stade of GOLD 2023 classification ANOVA F = 35,67 p = 0,001 (Figure 10).

Discussion

Several studies have shown that TFdi was lower in COPD than in healthy individuals.

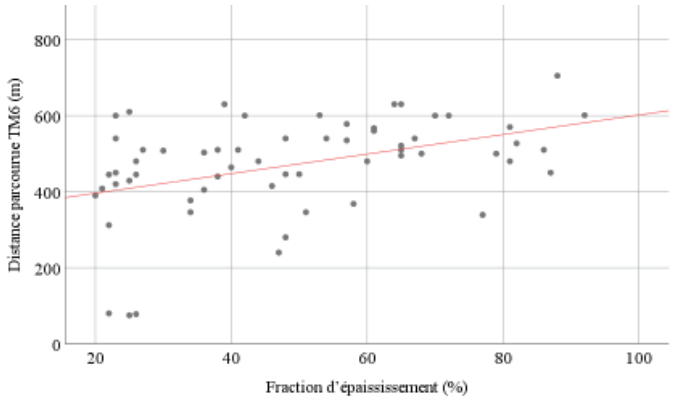
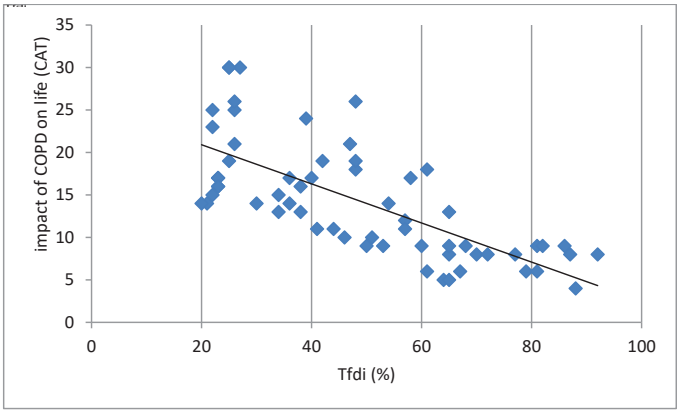


Figure 7: Simple dispersion with TFdi adjustment curve by the distance covered in the six-minute walking test.



Coefficient PEARSON = - 0,717 ; p = 0,000 .

Figure 8: Simple dispersion with TFdi adjustment curve by the CAT.

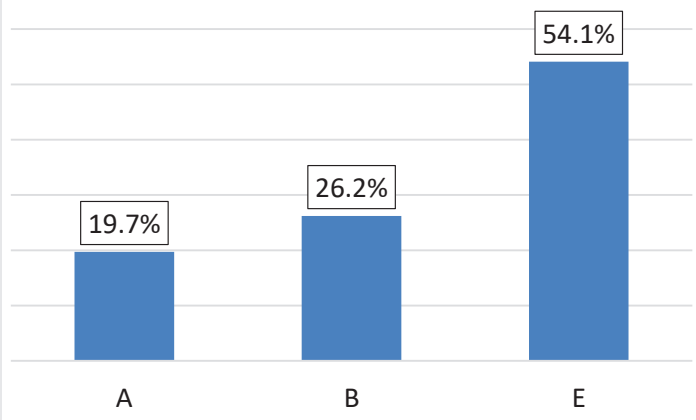


Figure 9: Patient distribution according to GOLD 2023 classification.

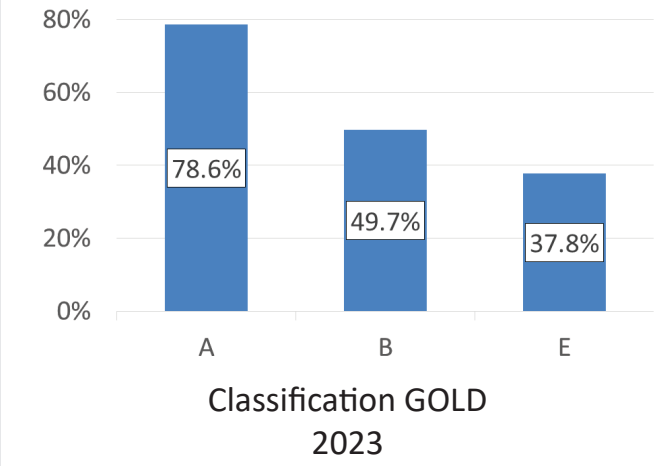


Figure 10: Mean of the Tfdi according to different stade of GOLD 2023 classification.

Our results highlight the negative influence of COPD on TFDi, in our PBCO cohort the mean of the TFDi is 48.92 +/- 21.06% and it is lower than the results found in the literature for healthy subjects [20-28].

In our study, we observed a highly significant negative correlation between the TFdi and the mMRC dyspnea score (r = -0.591, p <.). This means that the lower the TFdi, the higher the dyspnea score, indicating more severe dyspnea. These results suggest that decreased TFdi, reflecting reduced diaphragmatic contractility, could be associated with increased respiratory limitation in patients with COPD. These results are consistent with the observations of Abd El-Fattah, et al. [29], who reported similar findings in a study of 40 patients with stable COPD. They also found a significant negative correlation between the TFdi and the severity of dyspnea, measured using the mMRC scale, reinforcing the idea that reduced diaphragmatic contractility directly contributes to the sensation of dyspnea in these patients.

The relationship between TFdi and dyspnea can be explained by functional and structural alterations of the diaphragm in COPD patients, particularly due to pulmonary hyperinflation. Chronic hyperinflation tends to flatten the diaphragm, reducing its mechanical efficiency and ability to generate sufficient pressure for adequate ventilation [30].

However, it is important to note that not all studies reach the same conclusions. For example, the study of Eryüksel, et al. [31] did not find a significant correlation between the TFdi and mMRC score in their cohort of COPD patients. These differences may be due to methodological variations, differences in population samples, or COPD stages studied.

In our study, a highly significant negative correlation was observed between the CAT score and the TFdi (r = -0.717, p < 0.001). This result suggests that the lower the TFdi, the higher the impact of COPD on patients' quality of life as measured by the CAT score. This association highlights the link between diaphragmatic function and perception of COPD symptoms, highlighting the importance of the diaphragm as a key indicator in assessing clinical severity.

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The results of our study are consistent with those reported by Wendpap CDR, et al. [32] in a 2021 Brazilian study, which also demonstrated an inverse correlation between diaphragm thickness and the health status of patients with moderate to severe COPD (r = -0.735, p = 0.004). This consistency between the different studies highlights the importance of TFdi as a functional biomarker in assessing the clinical consequences of COPD.

The CAT score is a validated tool that assesses the impact of COPD on patients' daily lives. A decrease in TFdi, indicating lower diaphragmatic contractility, is likely to contribute to fatigue of the respiratory muscles, thus aggravating these symptoms. Diaphragmatic weakness limits the ability of patients to generate adequate respiratory volumes, leading to increased dyspnea and a decrease in quality of life.

However, some studies have not found a significant correlation between the TFDi and CAT score. Eryüksel E, et al. [31] Topcuoglu C, *et* al. [33] for example, did not observe a statistically significant relationship between these two parameters. The observed variations in results could be attributed, as for the mMRI dyspnea score, to differences in methodological protocols, the size of the cohorts studied, or even to the stages of COPD taken into account. It is also possible that other factors, such as the presence of comorbidities or individual variability in symptom perception, may influence the results.

In our analysis, a significant negative correlation was objectified between the TFdi and the classification of COPD according to the GOLD 2023 classification (ANOVA F = 35.678, p < 0.001).

After a thorough literature review, it appears that no publication to date has investigated the relationship between TFdi and the new ABE classification of COPD.

A study conducted in Egypt by Essawy T [25], out of 80 patients with COPD showed significant correlations between the TFdi and the old ABCD classification (ANOVA F = 55.037, p = 0.001).

Our study found a significant positive correlation between the diaphragmatic thickening fraction (FDi) and Body Mass Index (BMI) (r = 0.374, p = 0.003). This link indicates that in patients with COPD, an increase in BMI may be associated with better diaphragmatic performance. These results corroborate those of the study conducted by Elsawy SB in 2017, which also demonstrated a similar positive correlation (r = 0.32, p = 0.001).

Hafez and Abo-Elkheir (2017) also confirmed this relationship in Egypt, showing that TFdi, both right and left, was positively correlated with BMI (r = 0.95, p = 0.001), thus reinforcing the idea of an interaction between body mass and diaphragmatic function. The hypothesis that a higher BMI could reduce the negative impact of COPD on respiratory muscle function is supported by these observations. The BMI may therefore have a protective impact on diaphragmatic function under certain conditions of COPD. However, it is interesting to note that some studies, such as those d'Eysa AM, et al. [34] Eryüksel E, et al. [35], did not find a significant correlation between the TFDi and BMI.

We also identified a significant positive correlation between pre-bronchodilator Forced Vital Capacity (FVC) and TFdi (TFdi) (r = 0.256, p = 0.047). This link indicates that lung capacity, as measured by FVC, may influence diaphragmatic function. A study by Topcuoglu C, et al. in Turkey [33], also showed a similar relationship (r = 0.364, p = 0.048), reinforcing the idea of an interrelation between diaphragm performance and lung capacity in this population.

Our study showed a significant positive correlation between FEV1 and the diaphragmatic thickening fraction (r = 0.418, p = 0.001). These results are closely aligned with the work of Lim, et al. [36], which showed a strong correlation between TFdi and FEV1 in patients with stable COPD (r = 0.89, p = 0.017).

Other studies, such as those conducted by Eysa AM, et al. [34], also reported similar correlations between Tfdi and FEV1 (r = 0.26, p = 0.008).

A positive correlation was also found in our series between the FEV1/FVC ratio (%) and the TFDi (r = 0.448, p <.). These results are similar to those reported by Elsawy SB [37] in 2017, which showed a positive correlation between the TFdi and the FEV1/FVC ratio (%) (r = 0.29, p = 0.02). Similarly, a recent study in Egypt by Eysa AM, et al. [34] in 2023 confirmed this correlation (r = 0.32, p = 0.001).

A study conducted in Russia by Volchkov V, et al. [38] in 2016 showed a significant negative correlation between TFdi and PaO_2 (r = -0.42, p < 0.05). Contrary to their results, our study did not find a significant correlation between TFDi and PaO_2 (r = -0.202, p = 0.118). This may be explained by the difference in severity of COPD between the two groups studied, as Volchkov et al. included 60 patients with GOLD III and IV COPD, 26 of whom had severe hypoxemia (PaO_2 = 53.9 5.9 mmHg), while our study included patients with less advanced stages of COPD.

In our study, we observed a significant correlation between the TFdi and the distance traveled during the 6-minute walking test (TM6), with a value of r = 0.419 and p = 0.001. These results show that the higher the TFdi, the better the exercise capacity, measured by the distance traveled at TM6.

Hafez MR and OI Abo-Elkheir [39] reported similar findings, finding a strong positive correlation (r = 0.95, p = 0.001) between the TFdi and the distance traveled at TM6 in patients with COPD. Their study confirms that diaphragmatic function is a major determinant of physical performance in these patients and that a better diaphragmatic thickness is associated with an improvement in the tolerance to effort.

The relationship between TFdi and exercise capacity, assessed by TM6, highlights the importance of the diaphragm in respiratory efficiency, especially in conditions of pulmonary hyperinflation such as COPD [40]. The diaphragm, as the main inspiratory muscle, suffers structural and functional alterations in these patients, partly due to air trapping and hyperinflation.

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These changes decrease the ability of the diaphragm to contract effectively, limiting exercise capacity. A lower TFdi is often the reflection of diaphragmatic dysfunction, and an accurate assessment of the TFdi could therefore serve as a prognostic indicator for performance at TM6.

Conclusion

Diaphragmatic ultrasound is a valuable tool for assessing the morphology and function of the diaphragm in patients with COPD. It is therefore suggested that this examination should be systematically integrated into the management of patients, especially those with dyspnea symptoms. Ultrasound, being a non-invasive technique, could be used as an early detection tool to identify patients at risk for diaphragmatic dysfunction even in the early stages of COPD.

One of the major contributions of this study is the demonstration of morphological alterations of the diaphragm in COPD patients, including thinning of the diaphragmatic muscle. This is particularly significant in the advanced stages of the disease. The thinning of the diaphragm, observed by ultrasound, is largely explained by pulmonary hyperinflation, which flattens and stretches the diaphragm, placing it in a situation of mechanical disadvantage. This morphological alteration prevents the diaphragm from functioning effectively as the main inspiratory muscle, contributing to the dyspnea symptoms that COPD patients frequently report.

The decrease in TFdi reflects a loss of diaphragmatic mobility, exacerbated by the limitation of respiratory volumes in these patients. These findings support previous work that suggests that diaphragmatic dysfunction plays a crucial role in the worsening of clinical symptoms, including dyspnea and intolerance to exercise.

Finally, the study established significant correlations between morphological and functional parameters of the diaphragm and various clinical and functional indicators. Thus, the reduction in diaphragmatic thickness is correlated with the severity of COPD according to the GOLD classification. The more advanced the disease, the more pronounced the diaphragmatic dysfunction.

Declaration

Ethical compliance: The research experiments conducted in this article with animals or humans have been approved by the ethics committee and the authorities responsible for our research organizations, following all guidelines, regulations, and legal and ethical standards required for Humans or animals.

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Contributions from authors

A. Meridj, Designed and developed the analysis; and Written the article.

R. Belala, Collected data;

Y. Djeghri Conducted the analysis.

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