PROTOCOL DESIGN

Exploring Diaphragmatic Ultrasonography as a Diagnostic Tool for Hyperinflation in COPD Patients: A protocol study

Exploration de l'échographie diaphragmatique comme outil de diagnostic de l'hyperinflation chez les patients atteints de BPCO: Protocole de recherche

Hela Cherif[1], Chirine Moussa[2], Islam Mejri[3], Salma Mokaddem[1], Soumaya Debiche[1], Manel Ben Fradj[4], Zied Moatemri[3], Mohamed Ridha Charfi[1]

1. Tunis El Manar University, Faculty of Medicine of Tunis, Internal Security Forces Hospital, Pulmonology Department; Health and environment in security forces research laboratory LR211NT01, Tunis; Tunisia
2. Tunis El Manar University, Faculty of Medicine of Tunis, Military Hospital, Pulmonology department, Tunis; Tunisia
3. Tunis El Manar University, Faculty of Medicine of Tunis; Abderrahmane Mami Hospital, Pavillon I Pulmonology department, Ariana; Tunisia
4. Faculty of Medicine of Monastir

Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a widespread global health problem marked by chronic inflammation, emphysematous lung damage, and persistent airflow limitation. In COPD, hyperinflation exacerbates respiratory muscle weakness by causing diaphragmatic dysfunction. Diaphragmatic ultrasonography (US) is a non-invasive tool for evaluating diaphragmatic function, which may provide insight into the severity of hyperinflation in COPD. The purpose of this study is to evaluate the effectiveness of diaphragmatic ultrasonography in assessing lung hyperinflation in patients with COPD .

Methods: A diagnostic cross-sectional investigation will be carried out in two Tunisian pulmonology centers. COPD patients aged ≥40 years with confirmed diagnosis via spirometry and stable clinical status will be included. Exclusion criteria are other chronic respiratory diseases, neuromuscular diseases, or obesity. Diaphragmatic ultrasonography and whole-body plethysmography will be performed on the patients. During deep inspiration and forceful expiration, the diaphragmatic thickness and thickening fraction will be measured. RV > upper limit of normal (ULN) indicates lung hyperinflation. Pearson's or Spearman's correlation will be used to assess relationships between plethysmographic parameters and diaphragmatic ultrasound results. Diaphragmatic ultrasonography's diagnostic thershold for hyperinflation will be determined using ROC (receiver operating characteristic) curves.

Conclusion: If proven effective, diaphragmatic ultrasound could be a practical and cost-effective alternative to plethysmography for diagnosing hyperinflation in COPD.

Key words: Diaphragmatic Ultrasonography, Hyperinflation, COPD, Respiratory Function Respiratory Muscles, Diaphragm Dysfunction

Résumé

Introduction: La bronchopneumopathie chronique obstructive (BPCO) est un problème de santé mondial très répandu, marqué par une inflammation chronique, de l'emphysème et une limitation persistante des débits. Dans la BPCO, l'hyperinflation exacerbe la faiblesse des muscles respiratoires en provoquant un dysfonctionnement diaphragmatique. L'échographie diaphragmatique est un outil non invasif permettant d'évaluer la fonction diaphragmatique et la gravité de l'hyperinflation, par conséquent.

Le but de cette étude sera d'évaluer l'efficacité de l'échographie diaphragmatique dans l'évaluation de l'hyperinflation pulmonaire chez les patients atteints de BPCO.

Méthodes: Une enquête diagnostique transversale sera menée dans deux centres tunisiens de pneumologie. Les patients atteints de BPCO, âgés de ≥40 ans, dont le diagnostic a été confirmé par spirométrie et dont l'état clinique est stable, seront inclus. Les critères d'exclusion sont d'autres maladies respiratoires chroniques associées, des maladies neuromusculaires ou l'obésité. Les patients seront soumis à une échographie diaphragmatique et à une pléthysmographie. L'épaisseur du diaphragme et la fraction de raccourcissement seront mesurées au cours d'une inspiration et d'une expiration profonde. Un volume résiduel supérieur à la limite supérieure de la normale indique une hyperinflation pulmonaire. La corrélation de Pearson ou de Spearman sera utilisée pour évaluer les relations entre les paramètres pléthysmographiques et les résultats de l'échographie diaphragmatique. Le seuil diagnostique échographique pour l'hyperinflation sera déterminé à l'aide de la courbe ROC .

Conclusion: Si son efficacité est prouvée, l'échographie diaphragmatique pourrait constituer une alternative pratique et rentable à la pléthysmographie pour diagnostiquer l'hyperinflation au cours de la BPCO.

Mots clés: Échographie diaphragmatique, hyperinflation, BPCO, fonction respiratoire, muscles respiratoires, dysfonctionnement du diaphragme

Correspondance
Hela Cherif
Internal Security Forces Hospital, Pulmonology department, Tunis, Tunisia
Email: hela_cherif@hotmail.com

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Introduction

One of the major global health concerns is chronic obstructive pulmonary disease (COPD). The current worldwide prevalence is 11.7% (1). Chronic inflammation, emphysematous lung damage, and persistent airflow limitation are its defining characteristics. COPD causes a steady decline in lung function, having a major influence on afflicted people's quality of life (2). Furthermore, it has been recognized that COPD affects not only the lungs but also other organs, particularly the respiratory muscles. Given that the diaphragm is the major inspiratory muscle, its failure contributes to loss of respiratory function in people with COPD. COPD obstructs the tiny airways and reduces expiratory flow, resulting in air entrapment. This hyperinflation causes the diaphragm to flatten (3).

Most research examining the causes of inspiratory muscle weakening in people with COPD has concentrated on the diaphragm. COPD patients have a reduced transdiaphragmatic pressure generation capacity than healthy people (4). This decrease has been linked to diaphragm dysfunction caused by hyperinflation, which puts the diaphragm in a mechanical disadvantage (5).

It has been consistently demonstrated that patients with severe COPD generate less maximal inspiratory pressure and transdiaphragmatic pressure, both voluntarily and through phrenic nerve stimulation (excluding central drive effects), compared to patients without COPD (4,6,7). Similowski and co-workers (6) posited that the diaphragm weakness observed in patients with COPD may be attributed to diaphragm shortening induced by hyperinflation. They revealed that, at equivalent lung volumes, some patients with COPD generated even higher transdiaphragmatic pressures than healthy subjects.

However, in addition to the mechanical explanation for diaphragm weakness in COPD, several studies have suggested structural adaptations in the diaphragm to be involved. The invasive evaluation of the human diaphragm has contributed to a better understanding of the pathogenesis of diaphragm weakness in COPD. The human diaphragm is chronically active and is among the most aerobically adapted striated muscles. In individuals with normal lung function, the diaphragm consists of a relatively high proportion (~50%) of type I fibers, compared to type IIa (~30%) and IIb (~20%) fibers (8,9). Therefore, patients with severe COPD and even those with mild-to-moderate COPD exhibit an increased proportion of type I fibers in the diaphragm, accompanied by a decreased proportion of fast, fatiguing fibers (type II) (8,10–12).

To effectively manage patients with COPD, it is imperative to investigate the diaphragm's function.

A number of techniques are currently used to evaluate diaphragm function, including X-ray, transdiaphragmatic pressure (Pdi), phrenic nerve stimulation, and electromyography (13,14). However, each of these procedures has drawbacks, such as radiation exposure, invasiveness, and technical difficulties. Ultrasound, on the other hand, is a rapid, simple, noninvasive, easy-to-perform, repeatable, inexpensive, and radiation-free examination technique widely used to diagnose and evaluate the severity of lung diseases in critical care medicine (15).

Standardized value of diaphragm thickness at rest in healthy young adults was reported with an average diaphragm thickness in men being 1.9 mm (95% CI: 1.7, 2.0mm) (16).

Furthermore, it was demonstrated that the diaphragm thickness and diaphragm thickening fraction in patients with COPD were significantly lower compared to those of healthy participants, suggesting diaphragm fiber injury and decreased contractility as possible factors. Therefore, diaphragm ultrasonography may provide a more comprehensive evaluation of diaphragm function in patients with COPD (17).

The diaphragm offset and thickening fraction in COPD patients were found to be lower than those in healthy controls and to be negatively correlated with the severity of the disease, according to a systematic review and meta-analysis carried out in 2022 and centered on the ultrasonographic evaluation of diaphragm function in patients with COPD. It is important to acknowledge that this meta-analysis has certain limitations, such as a limited number of included studies, significant heterogeneity among the studies, and inconsistent experience among ultrasound examiners (15).

Objective: The aim of this study is to explore the usefulness of diaphragmatic ultrasonography in evaluating hyperinflation in patients with chronic obstructive pulmonary disease. We aim to assess ultrasonography parameters (diaphragm thickness, thickening fraction), and its association with hyperinflation (RV, RV/TLC) in COPD patients.

Methods

Type of study

This is a cross-sectional diagnostic study, which will be carried out in two 3rd-line pneumology centers in Tunisia

Study population

The study population will consist of COPD patients aged 40 and over followed up at the consultation:

- Inclusion criteria: COPD confirmed by spirometry, clinically stable, no exacerbation in the last 3 months and willing to participate in the study.
- Non-inclusion criteria: the presence of a chronic respiratory disease other than COPD (asthma, obstructive hypopnea syndrome or bronchial dilatation), neuromuscular disease or obesity (body mass index > or = 30 kg/m2). Patients taking treatments that may affect diaphragmatic function, such as long-term antidepressants and corticosteroids.
- Exclusion criteria: unreliability of total body plethysmography or ultrasound interpretation (uncooperative patients, poor execution of total body plethysmography maneuvers and poor echogenicity, … etc.).

Two groups of patients will be considered :

LH+ : COPD patients with lung hyperinflation (LH) :

Residual volume (RV) and/or RV/Total Lung Capacity (TLC) > upper limit of normal (ULN) or > +1.64 (z-score)(18).
LH- : COPD patients without hyperinflation.
Participant timeline:
The study is scheduled to start in June 2025

Sample size

The formula used was designed for the calculation of the necessary sample size when conducting a comparative analysis of a novel diagnostic test against the established reference standard. This was applied to a cohort where both the true disease status and prevalence were known (19).

Formula :

$N= [Z_{\alpha/2}^{2} \times Se \times (1-Se) / i^2] / P$

- N : Estimated sample size
- Z: Standard normal deviate corresponding to a 0.5 % error (Zα/2 = 3.29 for a 0.05% significance level; α = 5%, Zα/2=1.96, Zα/22= 3.84)
- Se: Sensitivity determined from previous published data or clinician judgment.
- i: Desired precision, set as 7%
- P: Disease prevalence in the study population (e.g., the prevalence of hyperinflation in COPD patients = 0.73 (20)).

Using the values of Se = 0.5, i = 0.07, and a P = 0.61, the calculated sample size was N=268.

Data collection procedure

Clinical Data

Clinical data will be gathered by a physician through the utilization of a medical questionnaire (refer to Appendix 1). This questionnaire predominantly comprises closed-ended questions and will be administered in the Arabic language

Dyspnea

Dyspnea will be assessed using the modified Medical Research Council (mMRC) scale(21).
Symptoms evaluation:
The symptoms will be evaluated using the COPD Assessment Test (CAT). The assigned score will range from 0 (indicating an absence of symptoms) to 10 in highly symptomatic patients (22).

Whole Body Plethysmography (WBP)

WBP will be performed according to the 2005 American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations (23). The Cosmed Q-Box Body Plethysmography device will be employed for this purpose in both departments.
Plethysmograph calibration will be performed every morning after inputting temperature, humidity, and barometric pressure to correct the measurements to body temperature, barometric pressure, and water vapor saturation (BTPS). The calibration of pneumotach will be done using a three-liter syringe, while volume calibration will be automatic within an acceptable range defined by the manufacturer. Daily calibration verification will be at low, medium, and high flow.
The following variables: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), peak expiratory flow (PEF), forced expiratory flow between 25% and 75% of FVC (FEF25-75%), slow vital capacity (SVC), thoracic gas volume (TGV), residual volume (RV), total lung capacity (TLC), inspiratory capacity (IC), functional residual capacity (FRC), FEV1/FVC, and FEV1/SVC will be measured and/or calculated according to the latest international recommendations. Reference values will be based on the Global Lung Initiative (GLI) 2012 for spirometric parameters (24) and GLI 2021 for static lung volumes (25).
Each patient will undergo baseline forced spirometry, followed by total body plethysmography to measure non-mobilizable static lung volumes. After the administration of a bronchodilator, a second series of spirometry tests will be performed. The diagnosis of COPD will be made when the FEV1/CV ratio after bronchodilators is less than 0.7.
On plethysmography, lung hyperinflation is defined by a RV greater than the upper limit of normal (ULN) or greater than +1.64 on the z-score. If only the RV is elevated, this is stage 1 hyperinflation; if the FRC is also above the ULN, it's stage 2; and if the TLC is involved, it's stage 3 hyperinflation. Pulmonary hyperinflation also results in increased RV/TLC and FRC/TLC ratios, the latter being a hallmark of COPD. Air trapping is considered severe if the RV/TLC ratio exceeds 60% (18).
We will also study the response of static lung volumes to bronchodilators.
The clinician will instruct the patient to withhold bronchodilators before plethysmography, as follows (26):

- Short-acting β2-agonist (SABA) salbutamol : 4–6 h
- Short-acting muscarinic antagonist (SAMA), e.g., ipratropium bromide : 12 h
- Long-acting β2-agonist (LABA) e.g., formoterol or salmeterol : 24 h
- Ultra-LABA e.g., indacaterol, vilanterol, or olodaterol : 36 h
- Long-acting muscarinic antagonist (LAMA) e.g., tiotropium, umeclidinium, aclidinium, or glycopyrronium: 36–48 h.

Diaphragm excursion scan

A high frequency (7.5 Mhz) array probe will be used and measurements will be done in B-Mode.
The transducer will be placed on the chest wall during the examination, precisely next to the anterior axillary line and slightly above the lower edge of the ribcage, while the patient will be in a supine position. The diaphragm can be seen as a hypoechoic muscular layer surrounded by two hyperechoic connective tissue layers (peritoneum and parietal pleura) by positioning the transducer perpendicular to two adjacent ribs. This observation was made deep to the intercostal muscles connecting the two ribs.
The diaphragm thickness will be measured for each hemithorax during the two phases of forced expiration and maximal deep inspiration of the subject, and the average value will be taken from 3 scans.

The Diaphragm Thickening Fraction (DTF) is a measurement used to assess the function of the diaphragm (27) . It is calculated using the following formula:
Diaphragm Thickening fraction (%) =

$$\frac{\text{Diaphragm thickness at maximal inspiration (Tdi) - Diaphragm thickness at maximal expiration(Tde)}}{\text{Diaphragm thickness at maximal inspiration (Tdi)}} \times 100$$

This formula determines the percentage change in diaphragm thickness between the states of deep inspiration and deep expiration.

- Tdi refers to the diaphragm thickness at deep inspiration.
- Tde refers to the diaphragm thickness at deep expiration.

The DTF reflects the ability of the diaphragm to contract and expand, which is an important indicator of respiratory muscle function (28).

Study Protocol

The study protocol will proceed as follows:
1. Consultation at the pulmonology department
2. Completion of the medical questionnaire
3. Anthropometric measurements
4. Performance of whole body plethysmography
5. Performance of thoracic ultrasound by two qualified physicians who will be blinded to the results of the plethysmography.

Statistical Analysis

SPSS (version 26.0; SPSS) will be used for all of the analyses. Normally distributed measurement data are expressed as the mean±SD. The inspection level α was 0.05. Non-normally distributed data will be presented as the median [IQR]. Normally distributed measurement data will be compared between groups by the two-independent-sample t test. The Mann–Whitney U-test will be used for comparisons between groups that will not conform to the normal distribution. For count data, the chi-square test will be used for comparison between groups. Pearson's correlation coefficient will be calculated between ultrasound results and normally distributed pulmonary function measurement data. Spearman correlation coefficient will be calculated between ultrasound and non-normally distributed pulmonary function measurement data. The correlations will be compared by the Z test. Multiple linear regression analysis will be used to analyze the factors affecting DTF. Taking RV and/or RV/TLC > ULN as the criteria for the diagnosis of LH, receiver operating characteristic (ROC) curves of Diaphragmatic Thickenig fraction (DFT) for the diagnosis of LH will be constructed, and the corresponding sensitivity and specificity will be calculated. The area under the curve (AUC) will be determined. The diagnostic threshold that provides the best balance between sensitivity and specificity will be identified as the optimal operating point on the ROC curve. At this optimal operating point, the matching value of the DTF will serve as the suggested diagnostic threshold for hyperinflation in COPD patients. The test will measure the interobserver variability between the first and second observers' observations of the same subjects. The Kappa coefficient will be used to evaluate the reproducibility of the diagnostic test. Statistical significance will be defined as a p-value of less than 0.05.

Results

The main results will be summerized in tables (tables1,2 and 3)

Table 1. Clinical Characteristics

Characteristics	LH+	LH-	p
Age (years)			
Male subject, n (%)			
Body mass index (kg/m2)			
Smoking statut (%)			
· Past smoker			
· Current smoker			
· Never smoker			
Smoking (pack-years)			
mMRC score			
FEV1% predicted value			
FEV1/FVC (%)			
Obstruction severity, FEV1 post β2 (% predicted)			
· ≥ 80			
· 50 79			
· 30-49			
· <30			

Table 2. Ultrasound Characteristics of Study Participants

	LH+	LH-	p
Mean diaphragm thickness at maximal inspiration (Tdi)			
Mean diaphragm thickness at maximal expiration (Tde)			
Mean Diaphragmatic thickening Fractio (DTF)			

Table 3. Correlation Between Ultrasound Parameters and Pulmonary Function Indices Reflecting LH

	DTF		Tdi		Tde	
	r	p	r	P	r	p
RV						
TLC						
FRC						
IC						
RV/TLC						
IC/TLC						

Dissemination

To present the research findings at conferences, seminars, community forums, etc.

Conclusion

Thoracic ultrasonography examination for identifying thoracic hyperinflation using diaphragmatic excursion measurement is an essential study because it may provide a more practical and cost-effective alternative to whole-body plethysmography. The study's findings have important implications for identifying thoracic hyperinflation and treating patients with chronic obstructive pulmonary disease (COPD). If thoracic ultrasonography is found to be a helpful diagnostic tool for thoracic hyperinflation, it may be used more broadly in clinical practice to measure pulmonary function in COPD patients and establish their phenotype. This could lead to enhanced patient care and more targeted treatment solutions for those with COPD and thoracic hyperinflation.

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