RESPIRATORY CARE Paper in Press. Published on September 12, 2017 as DOI: 10.4187/respcare.05646

Diaphragmatic Thickness Fraction in Subjects at High-Risk for COPD Exacerbations

Emel Eryüksel MD, Canan Cimşit MD, Melahat Bekir MD, Çagatay Cimsit MD, and Sait Karakurt MD

BACKGROUND: Ultrasound-based diaphragmatic thickness fraction is a reflection of the size and function of the diaphragm. This study aimed to examine the value of this measurement in identifying patients with COPD who are at high risk for the development of symptoms and exacerbations. METHODS: This cross-sectional study included 53 subjects with COPD. Respiratory function test results, ultrasonography-based diaphragmatic thickness, symptom scores (modified Medical Research Council dyspnea scale); COPD Assessment Test results, and number of previous exacerbations and admissions were recorded. RESULTS: Only age showed an inverse and weak relation with percent thickness fraction ($r = -0.37$, $P = .006$). None of the other variables tested correlated significantly with percent thickness fraction. No association was found between percent thickness fraction and exacerbation frequency, modified Medical Research Council dyspnea scale and COPD Assessment Test symptom scores, or Global Initiative for Chronic Obstructive Lung Disease ABCD risk/symptom assessments. CONCLUSIONS: Diaphragmatic thickness fraction measurements based on diaphragmatic ultrasound assessment in subjects with COPD seemed to be unable to identify subjects at high risk of symptoms and exacerbations as defined by the Global Initiative for Chronic Obstructive Lung Disease ABCD composite disease index. *Key words: COPD; muscles; respiratory; diaphragm; work of breathing; imaging; radiology.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

COPD represents a major cause of morbidity and mortality globally that is associated with an enormous and ever-increasing social and economic burden to societies.[1] One objective of patient assessment in COPD is to determine the severity of the disease and the potential associated risks. The severity of the disease cannot be gauged on the basis of FEV_1 alone in COPD, which represents a clinically heterogeneous disorder.[2] It is increasingly recognized that clinical end points other than FEV_1 also carry prognostic significance, including the severity of dyspnea, exercise capacity, and body mass index.[3] Accordingly, there has been a recent interest in the use of composite indices for predicting prognosis in COPD, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, which have incorporated the combined use of symptoms and the risk of disease exacerbation as a means for improving COPD management (ABCD).[1] However, this approach, originally introduced in 2011 by GOLD, has been criticized for inadequate evidence. Further assessment tools using a variety of multiple parameters also have been proposed, such as the BODE,[3] ADO,[4] and DOSE indexes.[5]

Increased end-expiratory lung volume is associated with a significant burden on inspiratory muscles, and particularly on the major inspiratory muscle, that is, the diaphragm.[6] Ultrasound examination of the diaphragm for structural and functional assessments is increasingly used, allowing the measurement of the muscular thickness and

Drs Eryüksel, Bekir, and Karakurt are affiliated with the Department of Pulmonary and Critical Care, School of Medicine, Marmara University, Istanbul, Turkey; Drs Canan Cimşit and Çagatay Cimsit are affiliated with the Department of Radiology, School of Medicine, Marmara University, Istanbul, Turkey.

The authors have disclosed no conflicts of interest.

Correspondence: Emel Eryüksel, Marmara Universitesi Tip Fakultesi, Gogus Hastalikları ve Yogun Bakim A B D, Mimar Sinan Caddesi Fevzi Cakmak Mah, Üst Kaynarca Pendik Istanbul, Turkey. E-mail: dreryuksel@gmail.com.

DOI: 10.4187/respcare.05646

RESPIRATORY CARE Paper in Press. Published on September 12, 2017 as DOI: 10.4187/respcare.05646

excursions of the diaphragm.[7] However, diaphragmatic thickness measurements may be misleading despite normal functionality in individuals with lower body weight. Therefore, diaphragmatic thickness fraction has been proposed to avoid such misinterpretation. similar to the case with cardiac ejection fraction, diaphragmatic thickness fraction is a reflection of the size and functions of the diaphragm.[8,9] Diaphragmatic thickness fraction measurements have been reported to be useful in determination of lung hyperinflation in subjects with COPD.[10,11] Ultrasound-based diaphragmatic thickness fraction measurements have been reported to be useful in determination of lung hyperinflation in subjects with COPD.[10,11] In addition, diaphragmatic thickness fraction has been successfully used for predicting the outcome of weaning and extubation in subjects admitted to the ICU as well as in determining the respiratory effort and the contractile activity of the diaphragm.[9,12-15] Therefore, it may be a potential tool for the assessment of disease status and outcomes in patients with COPD.

This study was undertaken to determine the value of ultrasound-based diaphragmatic thickness fraction measurements in identifying the subjects at high risk of developing symptoms and exacerbations based on GOLD ABCD grading system.

QUICK LOOK

Current knowledge

Increased end-expiratory lung volume is associated with a significant burden on inspiratory muscles, and particularly on the diaphragm. Ultrasound-based diaphragmatic thickness fraction measurements have been reported to be useful in the determination of lung hyperinflation in subjects with COPD. In addition, diaphragmatic thickness fraction has been successfully used for predicting the outcome of weaning and extubation in subjects admitted to an ICU, as well as in determining the respiratory effort and the contractile activity of the diaphragm.

What this paper contributes to our knowledge

Diaphragmatic thickness fraction measurements based on diaphragmatic ultrasound assessment in subjects with COPD seemed to be unable to identify those at high risk for symptoms and exacerbations as defined by GOLD ABCD composite disease index, which may be explained by the chronic adaptive processes occurring in the diaphragms of patients with COPD. Although diaphragmatic thickness fraction has the potential to predict disease course or future risks in patients with COPD, findings of this study do not support its use for this purpose.

Methods

Subjects

The protocol for this cross-sectional study was approved by the institutional ethics committee (approval 09.2013.0204). A total of 53 subjects with COPD were included after providing written informed consent. The diagnosis of COPD was based on GOLD guidelines criteria.[1] Subjects included in the study were already receiving appropriate medical treatment for COPD and had a stable clinical course for at least 60 d before inclusion (ie, they had no exacerbations or hospital admission during that period). No subjects had a history of oral steroid or theophylline use. Exclusion criteria were as follows: significant reactivity after bronchodilator use (increase in $FEV_1 > 12\%$ of the baseline value and > 200 mL), inability to comply with study procedures, oxygen dependence, or history of abdominal/thoracic surgery.[16]

Respiratory function test results, ultrasonography-based diaphragmatic thickness, symptom scores (modified Medical Research Council dyspnea scale); COPD Assessment Test results, and number of previous exacerbations and admissions were recorded. All study tests were performed on the same day for each subject. Also, subjects were assessed clinically on the test day.

Pulmonary Function Tests

The pulmonary function tests were performed in the pulmonary function laboratory of Marmara University Hospital (Istanbul, Turkey) using a whole-body plethysmograph (Collins GS II, Collins, Braintree, Massachusetts). The FVC volume exhaled in 1 s during this maneuver and FEV_1/FVC were calculated, and the results were compared with reference values based on age, height, sex, and race.[1,17] A post-bronchodilator FEV_1/FVC of $< 70\%$ was considered to show air-flow obstruction.

Diaphragmatic Ultrasound

All subjects underwent B-mode ultrasound examinations in supine position. The examination was performed using a Logiq E9 (GE Healthcare, Milwaukee, Wisconsin) ultrasound system equipped with a 9–15 MHz linear transducer. The diaphragm was visualized by placing the transducer over the ninth intercostal space perpendicular to 2 ribs (eighth-tenth), between the anterior and the midaxillary lines where the zone of apposition can be observed optimally 0.5–2 cm below the costophrenic sinus. The

RESPIRATORY CARE Paper in Press. Published on September 12, 2017 as DOI: 10.4187/respcare.05646

hypoechoic diaphragm muscle was identified between 2 parallel echoic lines, namely the diaphragmatic pleura and the peritoneal membrane. Thickness was measured by placing the calipers inside the hyperechoic lines. The subject was instructed to breathe spontaneously. At least 3 images of the diaphragm thickness were recorded at end-expiration and were averaged for thickness evaluation. Averaged end-inspiration and end-expiration values were put into the following formula for calculation of percentage thickness fraction: % thickness fraction = [(thickness at end-inspiration) − (thickness at end-expiration)]/(thickness at end-expiration) × 100%.

Symptomatic Assessment

The symptom severity in study participants was assessed using the modified Medical Research Council dyspnea scale[18] and COPD Assessment Test.[19] The validity and reliability of the Turkish version of the latter scale has been shown previously.[20]

Composite Disease Grading Based on ABCD

Symptoms and/or the risk of exacerbations were assessed as proposed by the GOLD composite assessment system.[1] According to this composite index, a COPD Assessment Test score ≥ 10 is considered to signify the presence of high burden of symptoms. Although the COPD Assessment Test was preferentially used for symptomatic assessment, modified Medical Research Council dyspnea scale scores were used to determine the level of dyspnea (ie, a score ≥ 2 showing high burden of symptoms) when a COPD Assessment Test score was unavailable.

The risk of exacerbation was determined as follows: A high-risk category was assigned with a history of ≥ 2 exacerbations or hospital admission due to exacerbation within the past year. Based on this assessment, Group A consisted of subjects with low-risk, low-symptom burden; Group B, low-risk, high-symptom burden; Group C, high-risk, low-symptom burden; and Group D, high-risk, high-symptom burden. For statistical assessments, subjects in Groups C and D were considered high risk for exacerbations, and subjects in Groups B and D were considered high risk for symptoms.[1]

Statistical Analyses

SPSS (SPSS 21, Chicago, Illinois) was used for statistical analysis. Normality was tested using Shapiro-Wilk test and graphical methods. Data are presented in mean ± SD or *n* (%), where appropriate. Correlations between continuous variables were tested using Spearman's rho. Mann-Whitney U test was used to test the differences between 2 groups in terms of percent thickness fraction, and Kruskal-Wallis test was used to test the differences among more than 2 groups. A $P < .05$ was considered an indication of statistical significance.

Table 1. Subject Characteristics

Characteristics	Values
Age, mean ± SD y	62.6 ± 10.1
Male sex, *n* (%)	47 (88.7)
Smoking, mean ± SD pack-years	41.3 ± 26.7
Body mass index, mean ± SD kg/m^2	27.8 ± 5.1
No. of exacerbations within the last year, mean ± SD	1.5 ± 1.5
FEV_1/FVC, mean ± SD	58.1 ± 9.3
FEV_1, mean ± SD % predicted	67.0 ± 22.2
mMRC score, mean ± SD	1.7 ± 1.1
CAT score, mean ± SD	12.1 ± 7.7
Percent thickness fraction, mean ± SD	20.8 ± 12.3
ABCD distribution, *n* (%)	
A	13 (24.5)
B	19 (35.8)
C	4 (7.5)
D	17 (32.1)

N = 53.
mMRC = Modified Medical Research Council dyspnea scale
CAT = COPD Assessment Test

Table 2. Correlations of Percentage Thickness Fraction With Demographic and Clinical Data

Characteristics	r	*P*
Age	−0.37	.006
Body mass index	−0.22	.12
Smoking	0.10	.94
No. of attacks	−0.05	.72
FEV_1	0.18	.20
mMRC score	−0.14	.29
CAT score	−0.15	.26

mMRC = Modified Medical Research Council
CAT = COPD Assessment Test

Results

Table 1 shows subject characteristics. The majority of subjects were male (88.7%). Table 2 shows correlations of percent thickness fraction with demographical and clinical data. Only age showed an inverse and weak relation with percent thickness fraction ($r = -0.37$, $P = .006$). None of the other variables tested correlated significantly with percent thickness fraction (Table 2).

Table 3 shows percent thickness fraction by exacerbation risk and symptom levels according to different indices. Based on ABCD risk assessments for symptoms and exacerbations, around two thirds of subjects were at

RESPIRATORY CARE Paper in Press. Published on September 12, 2017 as DOI: 10.4187/respcare.05646

Table 3. Percentage Thickness Fraction by Exacerbation Risk and Symptom Levels According to Different Indices

Index	*n*	Percent Thickness Fraction (mean ± SD)	*P*
Frequency of exacerbations			.46
High*	22	19.6 ± 11.5	
Low	31	21.7 ± 13.0	
mMRC score			.35
High symptom (≥2)	24	19.3 ± 10.6	
Low symptom (<2)	29	22.2 ± 13.6	
CAT score			.33
High symptom (≥10)	30	20.8 ± 14.1	
Low symptom (<10)	23	20.9 ± 9.8	
ABCD symptom evaluation			.51
High symptom (B + D)	36	20.7 ± 13.0	
Low symptom (A + C)	17	21.1 ± 10.9	
ABCD exacerbation evaluation			.30
High risk (C + D)	32	19.3 ± 11.7	
Low risk (A + B)	21	21.9 ± 12.8	

* ≥2 exacerbations or at least 1 hospitalization for exacerbation during the last year.
mMRC = Modified Medical Research Council
CAT = COPD Assessment Test

high risk for each of these parameters. High- and low-risk/symptom groups for frequency of exacerbations, modified Medical Research Council dyspnea scale and COPD Assessment Test symptom scores, or ABCD risk/symptom groups did not differ with regard to percent thickness fraction. In addition, ABCD groups did not differ with regard to percent thickness fraction: 21.5 ± 12.4, 22.1 ± 13.3, 20.0 ± 4.5, and 19.1 ± 12.9, respectively, $P = .60$.

Discussion

The results of our study show that diaphragmatic thickness fraction measurements based on diaphragmatic ultrasound assessment in COPD subjects were unable to identify those at high risk for symptoms and exacerbations as defined by GOLD ABCD composite disease index. To our knowledge, this is the first study that assessed the association between diaphragmatic thickness fraction and disease severity, symptoms, and exacerbation frequency.

Recently, there has been a surge in the number of ultrasound examinations of the diaphragm because of the widespread availability of this practical and noninvasive assessment tool. Using this imaging modality, studies examining the diaphragm in subjects with asthma,[21] Duchenne muscular dystrophy[22] or cystic fibrosis[23] have been carried out. Also, the utility of diaphragmatic function assessment has been examined in ICU subjects and in subjects experiencing weaning difficulties.[9,12] The respiratory effort and the diaphragmatic contractile activity was successfully assessed using diaphragmatic thickness fraction, with additional findings suggesting that this measurement may also be used for the determination of respiratory workload.[13-15]

Diaphragmatic thickness fraction represents a more sensitive measurement than diaphragmatic thickness measurements. An analogy between cardiac ejection and increased diaphragmatic thickness during inspiration as an indirect measure of muscle fiber contractions also has been proposed. Similar to the cardiac ejection fraction, this reflects the diaphragmatic functions and magnitude of effort.[8,9]

In a study by Baria et al,[24] diaphragmatic thickness and thickening ratio were examined using B-mode ultrasound in 50 subjects with COPD and 150 healthy control subjects. These investigators found no difference in diaphragmatic thickness or thickening ratio between subjects with COPD and control subjects. In that study, diaphragmatic thickness was measured during end-expiration and maximum inspiration, and thickening ratio was calculated as the ratio between end-expiration and maximum inspiration. On the other hand, in our study diaphragmatic thickness fraction was used for the structural and functional assessment of the diaphragm as proposed by Gottesman and McCool.[25] In addition, Baria et al did not examine the clinical correlates of the diaphragmatic measurements.

Davachi et al,[26] in their study comparing 25 subjects with COPD and 25 healthy control subjects, detected statistically significant differences in terms of diaphragmatic motility between the 2 groups. Also in that study, diaphragmatic motility was associated with airway obstruction, but not with hyperinflation. Paulin et al,[27] on the other hand, observed decreased diaphragmatic motility in subjects with COPD as compared with healthy control subjects, which was associated with distance covered in the 6-min walk test. In a subgroup analysis based on the diaphragmatic motility distance, those with lower diaphragmatic motility had more dyspnea. Interestingly, in contrast with observations reported by Davachi et al,[26] diaphragmatic motility was associated with hyperinflation in that study.

Our study is at variance with those above-mentioned studies, because diaphragmatic thickness fraction reflecting the functional capacity of the diaphragm was measured. There may be some potential explanations for the absence of an observed association between diaphragmatic thickness fraction determined by diaphragmatic ultrasound in subjects with COPD and high-risk status for symptoms and exacerbations based on GOLD ABCD composite index. First, in most of the studies examining inspiratory muscular dysfunction in COPD, the main focus of interest was the diaphragmatic muscle, because the diaphragm is not only the major inspiratory muscle, but also represents the muscular structure that is most intensely affected by hyperinflation, the characteristic feature of COPD. In pa-

RESPIRATORY CARE Paper in Press. Published on September 12, 2017 as DOI: 10.4187/respcare.05646

tients with COPD, the diaphragm is overburdened against an increased mechanical load because of airway obstruction. It has been suggested that the resulting mechanical load may lead to a chronic endurance training-type effect on the diaphragmatic muscle. In a previous study,[28] subjects with COPD and chronic hyperinflation were able to produce higher maximal transdiaphragmatic pressures when compared with normal individuals. Diaphragmatic myofibrils exhibit an increased level of activity against an increased mechanical load, and undergo structural remodeling because of chronic adaptation.[29] In our study, this chronic adaptive process may be responsible for the absence of an association between this index and symptoms as well as exacerbations in this stable group of subjects. However, further studies focusing on the most severe COPD patients and/or on the prediction of severe exacerbations may help clarify the issue. In addition, the course of the respiratory muscle function over time using spirometry or arterial blood gas studies together with its association with diaphragmatic thickness fraction seems to merit further investigation.

Inability to account for the significant variations in the clinical course of COPD by FEV_1 alone has led to inclusion of exacerbations and comorbid conditions in GOLD guidelines as a result of their effect on the disease severity. Although this new assessment system represents a significant step in the assessment of the disease, studies have suggested that the GOLD-defined categories of ABCD do not necessarily have to reflect a linear increase in disease severity.[30] Furthermore, patients in Group D also were shown to exhibit a certain degree of heterogeneity.[31] In our study, subjects categorized according to GOLD ABCD scoring systems did not differ significantly with regard to diaphragmatic thickness fraction, which may result from this within-group heterogeneity.

Limitations of our study include the relatively small sample size as well as the absence of controls. Another limitation relates to the absence of transdiaphragmatic pressure measurements via esophageal or gastric transducer, which are considered the accepted standards for the assessment of diaphragmatic functions. However, a correlation between ultrasound-based diaphragmatic function, lung volume, and inspiratory pressure values was found.[25,32]

Considering the importance of risk prediction and treatment planning in patients with COPD, the ABCD system represents a large step forward; however, its reliability is questionable. Nevertheless, exacerbation frequency and symptom severity have been incorporated in the ABCD system and are both valuable in treatment planning. Novel methods with potential to predict disease course or future risks, or which may provide additional information, would be helpful in this regard, and diaphragmatic thickness fraction has such a potential. However, current findings of this study do not support its use for this purpose.

Conclusions

Diaphragmatic thickness fraction measurements based on diaphragmatic ultrasound assessment in subjects with COPD seemed to be unable to identify those at high risk for symptoms and exacerbations as defined by GOLD ABCD composite disease index. Chronic adaptive processes occurring in subjects with COPD and the heterogeneity within GOLD ABCD risk assessment system may be responsible for our failure to identify an association between diaphragmatic function and symptoms/exacerbation risk in this stable group of subjects.

REFERENCES

1. The Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2017.
2. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010;11:122.
3. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350(10):1005-1012.
4. Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Antó JM, Augustí AG, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet 2009;374(9691):704-711.
5. Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. Am J Respir Crit Care Med 2009;180(12):1189-1195.
6. De Troyer A. Effect of hyperinflation on the diaphragm. Eur Respir J 1997;10(3):708-713.
7. Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med 2013;39(5):801-810.
8. Wait JL, Nahormek PA, Yost WT, Rochester DP. Diaphragmatic thickness-lung volume relationship in vivo. J Appl Physiol (1985) 1989;67(4):1560-1568.
9. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax 2014;69(5):423-427.
10. Okura K, Kawagoshi A, Iwakura M, Sugawara K, Takahashi H, Kashiwagura T, et al. Contractile capability of the diaphragm assessed by ultrasonography predicts nocturnal oxygen saturation in COPD. Respirology 2017;22(2):301-306.
11. Iwasawa T, Takahashi H, Ogura T, Asakura A, Gotoh T, Shibata H, Inoue T. Influence of the distribution of emphysema on diaphragmatic motion in patients with chronic obstructive pulmonary disease. Jpn J Radiol 2011;29(4):256-264.
12. Ferrari G, De Filippi G, Elia F, Panero F, Volpicelli G, Aprà F. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. Crit Ultrasound J 2014;6(1):8.

RESPIRATORY CARE Paper in Press. Published on September 12, 2017 as DOI: 10.4187/respcare.05646

13. Vivier E, Mekontso Dessap A, Dimassi S, Vargas F, Lyazidi A, Thille AW, Brochard L. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med 2012;38(5):796-803.
14. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med 2015;41(4):642-649.
15. Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Crit Care 2015;19:161.
16. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948-968.
17. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338.
18. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54(7):581-586.
19. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34(3):648-654.
20. Yorgancioğlu A, Polatli M, Aydemir Ö, Yilmaz Demirci N, Kirkil G, Nayci Atiş S, et al. [Reliability and validity of Turkish version of COPD assessment test]. Tuberk Toraks 2012;60(4):314-320.
21. de Bruin PF, Ueki J, Watson A, Pride NB. Size and strength of the respiratory and quadriceps muscles in patients with chronic asthma. Eur Respir J 1997;10(1):59-64.
22. De Bruin PF, Ueki J, Bush A, Khan Y, Watson A, Pride NB. Diaphragm thickness and inspiratory strength in patients with Duchenne muscular dystrophy. Thorax 1997;52(5):472-475.
23. Pinet C, Cassart M, Scillia P, Lamotte M, Knoop C, Casimir G, et al. Function and bulk of respiratory and limb muscles in patients with cystic fibrosis. Am J Respir Crit Care Med 2003;168(8):989-994.
24. Baria MR, Shahgholi L, Sorenson EJ, Harper CJ, Lim KG, Strommen JA, et al. B-mode ultrasound assessment of diaphragm structure and function in patients with COPD. Chest 2014;146(3):680-685.
25. Gottesman E, McCool FD. Ultrasound evaluation of the paralyzed diaphragm. Am J Respir Crit Care Med 1997;155(5):1570-1574.
26. Davachi B, Lari SM, Attaran D, Ghofraniha L, Amini M, Salehi M, et al. The relationship between diaphragmatic movements in sonographic assessment and disease severity in patients with stable chronic obstructive pulmonary disease (COPD). J Cardiothorac Med 2014;2(3):187-192.
27. Paulin E, Yamaguti WP, Chammas MC, Shibao S, Stelmach R, Cukier A, Carvalho CR. Influence of diaphragmatic mobility on exercise tolerance and dyspnea in patients with COPD. Respir Med 2007;101(10):2113-2118.
28. Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. N Engl J Med 1991;325(13):917-923.
29. Levine S, Nguyen T, Kaiser LR, Shrager JB. Evaluating respiratory muscle adaptations: a new approach. Am J Respir Crit Care Med 2002;166(11):1418-1419.
30. Agusti A, Hurd S, Jones P, Fabbri LM, Martinez F, Vogelmeier C, et al. FAQs about the GOLD 2011 assessment proposal of COPD: a comparative analysis of four different cohorts. Eur Respir J 2013;42(5):1391-1401.
31. Sillen MJ, Franssen FM, Delbressine JM, Uszko-Lencer NH, Vanfleteren LE, Rutten EP, et al. Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: findings of the DICES trial. Respir Med 2013;107(8):1186-1194.
32. Sarwal A, Walker FO, Cartwright MS. Neuromuscular ultrasound for evaluation of the diaphragm. Muscle Nerve 2013;47(3):319-329.