Am J Physiol Regul Integr Comp Physiol 313: R620–R629, 2017.
First published September 13, 2017; doi:10.1152/ajpregu.00173.2017.

RESEARCH ARTICLE | *Respiration*

Obesity modulates diaphragm curvature in subjects with and without COPD

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Submitted 4 May 2017; accepted in fina form 8 September 2017

Boriek AM, Lopez MA, Velasco C, Bakir AA, Frolov A, Wynd S, Babb TG, Hanania NA, Hoffman EA, Sharafkhaneh A. Obesity modulates diaphragm curvature in subjects with and without COPD. *Am J Physiol Regul Integr Comp Physiol* 313: R620–R629, 2017. First published September 13, 2017; doi:10.1152/ajpregu.00173.2017.—Obesity is a common comorbidity of chronic obstructive pulmonary disease (COPD) and has been associated with worse outcomes. However, it is unknown whether the interaction between obesity and COPD modulates diaphragm shape and consequently its function. The body mass index (BMI) has been used as a correlate of obesity. We tested the hypothesis that the shape of the diaphragm muscle and size of the ring of its insertion in non-COPD and COPD subjects are modulated by BMI. We recruited 48 COPD patients with postbronchiodilator forced expiratory volume in 1 s (FEV1)-to-forced vital capacity (FVC) < 0.7 and 29 age-matched smoker/exsmoker control (non-COPD) subjects, who underwent chest computed tomography (CT) at lung volumes ranging from functional residual capacity (FRC) to total lung capacity (TLC). We then computed maximum principal diaphragm curvature in the midcostal region of the left hemidiaphragm at the end of inspiration during quiet breathing (EI) and at TLC. The radius of maximum curvature of diaphragm muscle increased with BMI in both COPD and non-COPD subjects. The size of diaphragm ring of insertion on the chest wall also increased significantl with increasing BMI. Surprisingly, COPD severity did not appear to cause significan alteration in diaphragm shape except in normal-weight subjects at TLC. Our data uncovered important factors such as BMI, the size of the diaphragm ring of insertion, and disease severity that modulate the structure of the ventilatory pump in non-COPD and COPD subjects.

respiratory mechanics; emphysema; obesity

SEVERAL STUDIES REPORTED alteration of diaphragm muscle in patients with chronic obstructive pulmonary disease (COPD). Ottenheijm and colleagues reported that maximum force generation of skinned diaphragm fiber was markedly reduced in patients with mild to moderate COPD (24). However, it contradicts the reports in animal models of emphysema showing no consistent evidence for loss of specifi diaphragm muscle force (10). Clanton and Levine suggested that diaphragm alterations in COPD are essentially due to the adaptive processes of a complex muscle responding to the changes to its mechanical environment rather than caused by a form of dysfunction (10). Therefore, assessing diaphragm shape and measuring its potential altered kinematics in COPD is critical to improve our understanding of diaphragm and chest wall remodeling. In addition, identifying key determinants of diaphragm shape in smokers and exsmokers without history of lung disease as well as COPD subjects is important in assessing respiratory muscle structure and consequently its function in health and disease.

A recent multicenter prospective cohort study of Genetic Epidemiology of COPD has clearly demonstrated that obesity is associated with increased morbidity in moderate to severe COPD (16). Those investigators showed that obesity is prevalent among individuals with COPD and associated with worse COPD-related outcomes, ranging from quality of life and dyspnea to reduced 6-min walk distance and severe acute exacerbation of COPD. Guenette and colleagues reported that obese patients with COPD were not at a disadvantage during exercise relative to lean COPD patients (14). Those investigators argued that obesity may contribute to better survival in COPD patients due to reduced lung volume and higher inspiratory capacity-to-total lung capacity ratio compared with those of the normal weight COPD patients (14). Another complementary study by Ora and colleagues suggested that obese COPD patients had greater static recoil and intra-abdominal pressure, similar operating lung volumes, and similar ventilatory efficienc relative to those of lean COPD subjects during exercise (22). However, the data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End points (ECLIPSE) study showed more dyspnea and lower health status in obese COPD subjects compared with those of normal weight (3).

The main goal of our study was to evaluate the effects of obesity and COPD on the structure of the diaphragm and the size of its ring of insertion on the chest wall. Another objective was to examine whether obesity modulates the effects of the severity of the disease on both diaphragm shape and the size of its ring of insertion, as assessed by the forced expiratory volume in 1 s (FEV_1) as a percentage of predicted normal. We assessed diaphragm shape by computing the reciprocal of maximum principal curvature (radius of maximum principal curvature, R_{max}). In addition, we assessed chest wall remodeling by measuring the size of the diaphragm ring of insertion at the lower rib cage, over the physiological range from functional residual capacity (FRC) to total lung capacity (TLC) in subjects with mild to very severe COPD as well as subjects who were smokers or exsmokers without history of lung disease. The balance between the mechanical effects of hyperinflatio in COPD with effects of lung deflatio caused by obesity is important in assessing diaphragm structure and

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kinematics of the chest wall particularly at low lung volumes. The potential for a reduction in lung volume that is potentially caused by obesity could contribute to altered structure of the diaphragm as well as altered chest wall kinematics in COPD. We tested the hypothesis that the shape of the diaphragm muscle and size of the ring of its insertion in non-COPD and COPD subjects are modulated by body mass index (BMI).

METHODS

Study population. This was a cross-sectional study on subjects with COPD and age-matched smoker/exsmoker control subjects with normal lung function (non-COPD). Two groups of 48 COPD patients and 29 controls were recruited at the Michael E. DeBakey Houston Veterans Affairs Medical Center (HVAMC) and at the University of Iowa. Table 1 describes subjects' demographics. All subjects were 40 yr old or older and either current or exsmokers of at least 10 packs per year. Control subjects did not have any history of lung disease. COPD subjects demonstrated a postbronchodilator forced expiratory volume in 1 s (FEV1)-to-forced vital capacity (FVC) ratio (FEV1/FVC) of <70% of predicted. Control subjects had a baseline postbronchodilator FEV1 > 80% of predicted and FEV1/FVC ratio of >70% of predicted as well as being free from any significan disease as determined by history and physical exam and screening investigations. All subjects had to be able to comply with computed tomography (CT) imaging and lung function protocols as well as able to read, understand, and sign a consent form for the study.

Subjects with known history of significan inflammator disorders (e.g., lupus, rheumatoid arthritis), known to have severe α-1-antitrypsin deficiency have history of lung surgery, serious uncontrolled disease (including serious psychological disorder), or diagnosed with cancer except skin cancer were excluded. Subjects enrolled in a blinded drug study (open labeled studies and observational studies may be considered if they do not interfere with study procedures or increase risk of radiation exposure); those with evidence of alcohol and drug abuse were also excluded. COPD subjects with known respiratory disorders other than COPD, history of severe exacerbation within the last 4 wk before the study entry, chronic use of oral corticosteroids, and inability to walk were excluded.

All subjects were diagnosed based on the Global Initiative for COPD (GOLD) staging criteria (mild ≥ 80% of predicted, moderate = 50−80% of predicted, severe 30−50%, and very severe <30% of predicted) (1) (stage I, FEV1/FVC < 70%; FEV1 > 80% predicted; stage II, worsening of airflo limitation, FEV1/FVC < 70%; 50% < FEV1 < 80% predicted; stage III, further worsening of airflo limitation (FEV1/FVC < 70%; 30% < FEV1 < 50% predicted; stage IV, severe airflo limitation (FEV1/FVC < 70%; FEV1 < 30% predicted) or FEV1 < 50% predicted plus chronic respiratory failure (30). All subjects were stable clinical condition with no change in respiratory medications within the last 4 wk before enrollment in the study. The subject's height and weight were determined. The BMI [a person's weight (in kilograms) divided by the square of his or her height (in meters)] was used to defin the following three groups: normal weight (subjects with a BMI between 18.5 kg/m^2 and less than 25 kg/m^2); overweight (subjects with a BMI between 25 kg/m^2 and less than 30 kg/m^2); and obese (subjects with a BMI greater than 30 kg/m^2).

This study was approved by the Institutional Review Boards at Baylor College of Medicine and University of Iowa.

CT imaging of subjects. Subjects underwent simple spirometry tests while lying supine in the CT scanner. For chest CT, each subject was instructed to breathe through a mouth piece connected to a pneumatic flowmeter from which a computer program monitored flo to give expired and inspired tidal volume. The breathing tube did not have significan resistance; thus, it did not cause increased dyspnea. Before the CT image acquisition, subject's vital capacity and residual volume were determined. After mouth breathing for at least three tidal cycles, the subject was asked to take a deep inspiratory breath and a deep expiratory breath to determine the vital capacity. We repeated this process at least twice such that at least two vital capacity maneuvers were within 10% of each other. Residual volume was determined before each scan, whereas vital capacity was determined only once at the beginning of the protocol. In addition to the CT images collected at FRC and TLC. A subset of the subjects had CT imaging performed at both FRC and end of inspiration during quiet breathing (EI). We analyzed the performances of three deep inspiratory maneuvers immediately before scanning to ensure standardized expansion and ventilation for all subjects. While monitoring the subject's breathing, each subject was instructed to hold his/her breath at certain lung volumes for 10 s while CT imaging of the chest was performed using a 64-slice CT scanner.

We correlated both functional severity of COPD based on FEV1 and severity of COPD based on radiological measurements of emphysema with R_{max}. The severity of airflo limitation was determined by measuring FEV1 using a standard spirometry technique. We define emphysema severity as a percentage of total lung volume that contains voxels with densities below attenuation values less than or equal to −950 Hounsfiel units (HU) on inspiratory images. This is also known as a percentage of low attenuation cluster analysis (−950 HU %LAA) (21).

Computing principal curvatures of the diaphragm. Our analysis focused on the midcostal region of the left hemidiaphragm, where the peak of the hemidiaphragm is located. We also analyzed the size of the ring of insertion by measuring the distance between the left chest wall insertion of the diaphragm to the sagittal midplane of the subject. We utilized our well-developed computational approach in assessing diaphragm curvature in the canine model (4, 5, 7, 13). Briefly a plane was fitte to all points in the midcostal region of the left hemidiaphragm by minimizing the sums of the squares of the distances between the points of the surface and the plane. The coordinates of the points on the diaphragm surface were transformed to a new coordinate system with the X' and Y' axes in the plane, and the Z' axis aligned in the normal direction to the plane was determined. The quadratic in *Eq. 1* was fitte to the X' Y' Z' data by a multiple least-squares regression technique. Principal coordinates Z', X'', and Y'', were determined, for which the quadratic form is presented in *Eq. 2*, where K_{max} and K_{min} are the principal curvatures of the quadratic fit and Z' was a quadratic function of the X'', Y'' data. X'' was chosen as the coordinate along the largest principal curvature. The smaller principal curvature is therefore oriented along Y''.

$$Z' = aX'^2 + bX'Y' + cY'^2 + dX + eY' + F \quad (1)$$

$$Z' = \frac{1}{2}K_{max}X''^2 + \frac{1}{2}K_{min}Y''^2 + F' \quad (2)$$

where a, b, c, d, and e are coefficient of the quadratic function with at least one of a, b, and c not equal to zero. F and F' are constants. The details of the algorithm utilizing these equations are outlined in our earlier published report (5). For convenience, maximum principal curvature was converted by taking its reciprocal to compute the radius of maximum principal curvature, R_{max}.

Statistical analysis. Descriptive statistics were performed to examine the median, 25th, and 75th quartiles of the R_{max} and the size of the ring of insertion of the diaphragm on the chest wall in age-matched control non-COPD smoker and exsmoker subjects and COPD patients with different severity. Subjects within each group were stratifie according to their BMI, and differences between groups and within groups were assessed using an independent samples Mann-Whitney and Kruskal-Wallis Tests (IBM SPSS, version 24). All statistical tests used the criterion of significanc (α) of 0.05.

Table 1. *Demographics and lung functions of subjects with and without COPD*

Obesity Group	Age, yr	Gender Count	Ethnicity	Height, m	Weight, kg	BMI	FEV1/FVC, %	FEV1, liter	FEV1 %Predicted	TLC, liter	TLC %Predicted	RV, liter	RV % Predicted	Emphysema Severity (HIST 950), %
							Non-COPD							
Normal weight	54.0 ± 8.2	Male: 7 Female: 3	Caucasian = 10	1.7 ± 0.1	68.5 ± 6.2	22.6 ± 1.2	75.1 ± 2.9	3.4 ± 0.8	97.8 ± 9.2	6.5 ± 2.8	113.5 ± 22.1	2.8 ± 1.3	132.9[2] ± 59.7	0.13*
Overweight	56.4 ± 7.2	Male: 7 Female: 3	Caucasian = 5 African-American = 4 Hispanic = 1	1.7 ± 0.1	79.1 ± 7.6	27.7 ± 1.5	84.8 ± 3.8	2.9 ± 0.9	98.8 ± 27.6	5.2 ± 2.6	96.5 ± 26.815	2.2 ± 0.9	113.8 ± 43.8	0.3 ± 0.1
Obese	56.6 ± 10.1	Male: 5 Female: 4	Caucasian = 6 African-American = 3	1.7 ± 0.1	95.7 ± 13.3	33.3 ± 3.2	63.5 ± 36.4	2.9 ± 0.7	97.9 ± 15.3	6.1 ± 1.4	100.3 ± 14.8	2.4 ± 0.8	99.8 ± 28.6	1.1 ± 0.9
							Mild-to-Moderate COPD							
Normal weight	54.8 ± 7.5	Male: 4 Female: 1	Caucasian = 3 African-American = 1 Unknown = 1	1.8 ± 0.1	69.9 ± 8.9	22.3 ± 0.8	64.6 ± 5.8	2.9 ± 0.636	78.4 ± 1.3	7.5 ± 1.3	111.4 ± 11.3	3.0 ± 00.7	142.6 ± 42.3	1.9 ± 1.1
Overweight	64.9 ± 5.6	Male: 6 Female: 1	Caucasian = 7	1.8 ± 0.1	84.7 ± 7.2	27.2 ± 1.2	53.4 ± 9.2	1.9 ± 0.3	56.1 ± 5.7	7.2 ± 1.8	107.0 ± 22.4	3.3 ± 1.0	142.9 ± 41.3	8.8 ± 9.6
Obese	63.5 ± 5.0	Male: 9 Female: 1	Caucasian = 9 African-American = 1	1.7 ± 0.1	118.8 ± 23.8	39.6 ± 7.0	64.4 ± 6.4	2.0 ± 0.6	64.4 ± 15.1	6.4 ± 1.5	98.5 ± 24.1	3.1 ± 1.2	139.1 ± 55.4	1.8 ± 2.6
							Severe-to-Very Severe COPD							
Normal weight	63.5 ± 1.9	Male: 4 Female: 0	Caucasian = 2 African-American = 2	1.8 ± 0.1	64.2 ± 14.8	20.7 ± 2.4	43.0 ± 3.7	1.2 ± 0.1	36.5 ± 4.2	6.9 ± 0.1	107.3 ± 7.8	3.8 ± 0.5	177.3 ± 37.8	18.7 ± 12.8
Overweight	63.5 ± 7.0	Male: 9 Female: 1	Caucasian = 6 African-American = 3 Unknown = 1	1.8 ± 0.1	85. Three ± 7.6	27.1 ± 1.2	42.0 ± 8.5	1.3 ± 0.4	38.9 ± 8.2	7.3 ± 1.4	106.5 ± 19.9	3.6 ± 1.3	156.9 ± 55.9	16.7 ± 11.5
Obese	63.8 ± 5.2	Male: 9 Female: 3	Caucasian = 8 African-American = 3 Unknown = 1	1.8 ± 0.1	109.2 ± 12.5	36.1 ± 4.5	48.5 ± 10.7	1.1 ± 0.3	34.8 ± 9.2	7.1 ± 1.7	107.7 ± 19.1	4.5 ± 1.6	198.3 ± 64.6	6.2 ± 6.1

The data are shown (means ± SE) for three groups: normal weight, overweight, and obese for non-chronic obstructive pulmonary disease (COPD) subjects as well as two groups of COPD subjects of disease severities: mild-moderate COPD as well as severe to very severe COPD subjects. Demographics include age, gender, ethnicity, height, weight, body mass index (BMI). Lung function data include forced expiratory volume (FEV)1/forced vital capacity (FVC), FEV1 (liters), FEV1 as % predicted, total lung capacity (TLC, liters), TLC as percent predicted, residual volume (RV) (liters), RV as percent predicted. Table also shows emphysema severity that is based on the percentage of lung with attenuation values that are less than or equal to −950 Hounsfiel units (HU) on inspiratory images (HIST950%).

AJP-Regul Integr Comp Physiol • doi:10.1152/ajpregu.00173.2017 • www.ajpregu.org

RESULTS

As demonstrated in Table 1, the firs group of mild/moderate COPD subjects has an FEV1 range between 80% and 50% of predicted normal. The second group of severe/very severe COPD subjects has an FEV1 range between 49% of predicted and less than 30% of predicted. Figure 1 shows the surface of the diaphragm for a supine non-COPD subject acquired at TLC. Points on the diaphragm surface are aligned with the direction of the maximum principal curvatures as well as points that are aligned with the direction of minimum principal curvatures. According to our prior work on the shape of midcostal region of the diaphragm in the canine model, lines of maximum principal curvatures are aligned with the direction of its muscle fibers In addition, lines of minimum principal curvatures are aligned in the plane of the surface with the direction orthogonal to the muscle fibe orientation (4, 5, 7, 13). We examined the relation between the presence or absence of COPD and BMI and their effect on R_{max} of the midcostal diaphragm. Data in Fig. 2*A* show R_{max} for two groups: non-COPD subjects and COPD subjects. The R_{max} of the diaphragm of non-COPD smokers were not significantl different from that of the COPD subjects, indicating that diaphragm shape, at least in the midcostal region, is not altered by COPD. Data in Fig. 2*B* show R_{max} for all subjects including non-COPD and COPD for the three different groups: normal weight, overweight, and obese. Interestingly, these data show significan differences between R_{max} of normal weight subjects and that of overweight subjects ($P = 0.021$) as well as between

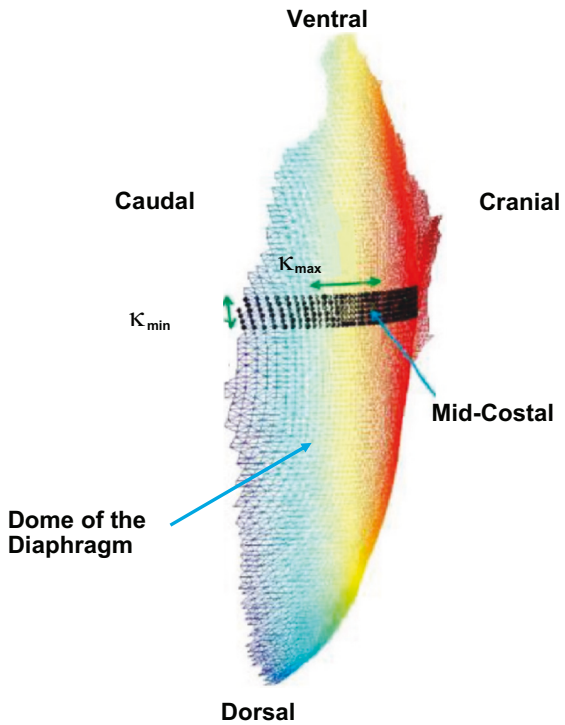

Fig. 1. The left hemidiaphragm surface is shown for a supine non-chronic obstructive pulmonary disease (COPD) subject at total lung capacity (TLC). The points on the surface of the midcostal diaphragm are aligned with the direction of the maximum principal curvatures (κ_{max}), which corresponds to the muscle fibe direction of the diaphragm. In addition, those points are also aligned with the minimum principal curvature (κ_{min}), which corresponds to the orthogonal direction to the diaphragm muscle fibers

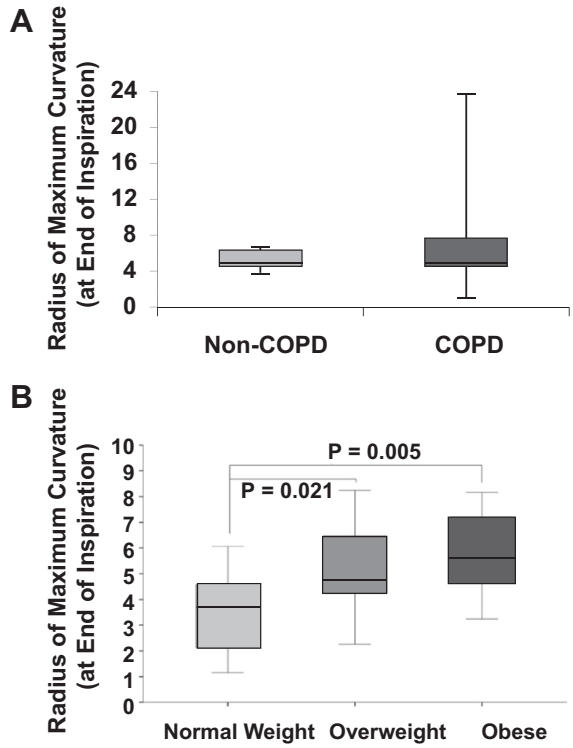

Fig. 2. *A*: box and whiskers plots of the radius of maximum curvature (R_{max}) in centimeter (cm) at end of inspiration during quiet breathing in two groups: non-COPD who are current or exsmoker subjects as well as COPD subjects. *Bottom* and *top* of the box are always the 25th and 75th percentile (the lower and upper quartiles, respectively), and the band near the *middle* of the box is the 50th percentile (the median). The "whiskers" shown above and below the boxes technically represent the largest and smallest observed scores that are less than 1.5 box lengths from the end of the box. There was large variability in R_{max} in the COPD group. Consequently, there is no significan difference between R_{max} of non-COPD and that of COPD subjects. These data show that at end of inspiration, diaphragm muscle shape of the midcostal region is not affected by COPD. *B*: box and whiskers plots of the R_{max} (in cm) at end of inspiration during quiet breathing in all subjects recruited in this study, including non-COPD subjects who are current or exsmokers as well as COPD subjects. The data are shown for three groups: normal weight, overweight, and obese. The data show significan difference in R_{max} between normal-weight and overweight subjects ($P = 0.021$) as well as between obese and normal weight subjects ($P = 0.005$).

R_{max} of obese subjects and that of normal weight subjects ($P = 0.005$). These data provide statistical evidence that regardless of the presence or absence of lung disease, diaphragm shape is significantl affected by BMI.

Data in Fig. 3 show that R_{max} at EI are significantl higher in those subjects of larger BMI for all COPD subjects as well as age-matched control non-COPD subjects. Normal-weight subjects show a significantl lower R_{max} than those for obese subjects among non-COPD smoker subjects ($P = 0.046$) and among COPD subjects ($P = 0.027$). Although not statistically significant the R_{max} of the diaphragm in overweight non-COPD subjects appeared to be greater than that of normal-weight subjects ($P = 0.083$), whereas R_{max} is significantl greater in obese subjects compared with R_{max} of normal-weight subjects ($P = 0.046$). There is a similar trend in COPD subjects. Although not statistically significant R_{max} of the diaphragm in overweight subjects appears to be greater than normal-weight COPD subjects ($P = 0.054$), whereas R_{max} is

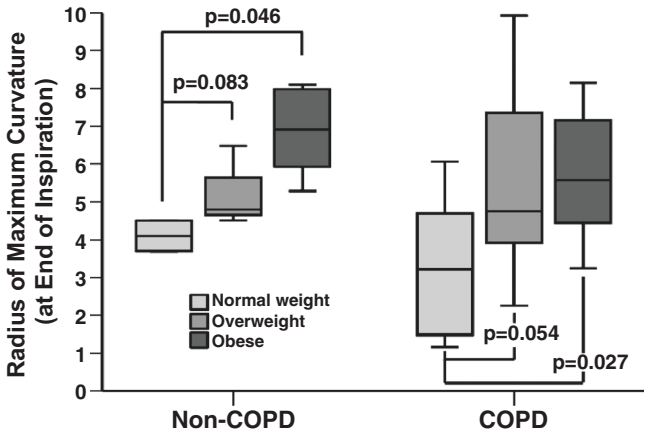

Fig. 3. Box and whiskers plots of the R_{max} (in cm) at end of inspiration during quiet breathing in smoker subjects with no history of lung disease COPD subjects. Data show R_{max} at end of inspiration (EI) is higher in those subjects of larger body mass index (BMI) for all COPD subjects as well as age-matched control smokers/exsmokers control subject (non-COPD). Normal-weight subjects show smaller R_{max} than those for obese subjects among non-COPD subjects ($P = 0.046$) and among COPD subjects ($P = 0.027$).

significantl greater in obese COPD than in normal-weight COPD subjects ($P = 0.027$). These data illustrate that diaphragm shape is modulated by BMI in COPD subjects as well as in smoker subjects with no history of lung disease.

Data in Fig. 4*A* show that R_{max} of obese subjects with mild/moderate COPD is significantl greater than that of the normal-weight group of similar disease severity ($P = 0.042$). Although there was an upward trend in R_{max} among severe/very severe subjects of different weights, there was a large variability in the group of normal-weight subjects, and this upward trend in R_{max} was not statistically significant We also evaluated the effect of using radiological measurements of emphysema to assess COPD severity on the relationship between disease severity and R_{max} for the three groups of BMI as shown in Fig. 4*B*. The R_{max} in severe/very severe COPD subjects appears to increase with BMI, although the difference did not reach significanc ($P = 0.064$).

At a higher lung volume such as TLC, no significan trend in R_{max} is observed among non-COPD and COPD subjects with increasing BMI as shown in Fig. 5*A*. Further analysis of COPD groups demonstrates a greater R_{max} with BMI in mild/moderate ($P = 0.039$), whereas BMI has no effect on R_{max} in the severe/very severe group (Fig. 5*B*). In normal-weight subjects, R_{max} is also found to be significantl larger in severe/very severe COPD subjects compared with those in mild/moderate COPD subjects ($P = 0.027$). At TLC, R_{max} in either overweight or obese subjects with mild/moderate COPD is not significantl different when compared with subjects with severe/very severe COPD.

The data in Fig. 6*A* show that at EI, the size of the ring of insertion is significantl smaller in normal-weight COPD subjects compared with either overweight COPD ($P = 0.005$) or obese COPD ($P = 0.008$). The data in Fig. 6*B* show a similar trend in mild/moderate COPD subjects with normal weight having smaller size of ring of insertion than either overweight ($P = 0.045$) or obese COPD subjects ($P = 0.019$). In contrast, there is no significan effect of BMI on the size of diaphragm ring of insertion in non-COPD subjects and subjects with severe/very severe COPD. At TLC, the size of diaphragm ring of insertion is not sensitive to BMI in non-COPD subjects. However, the diaphragm ring of insertion increases with increased BMI in the COPD group. The data in Fig. 6*C* show that obese COPD subjects have a significantl larger size of ring of insertion when compared with normal-weight COPD subjects ($P = 0.008$). Further analysis of COPD subjects show that mild/moderate COPD of the normal-weight group have significantly smaller size of ring of insertion than obese subjects of similar disease severity ($P = 0.004$) as depicted in Fig. 6*D*. Although not significant a similar trend is also observed between normal weight and obese subjects in the severe/very severe COPD group ($P = 0.09$).

A schematic of a model summarizing the effect of obesity and COPD on R_{max} and size of the ring of insertion at end of inspiration is shown in Fig. 7. The model was modifie from a

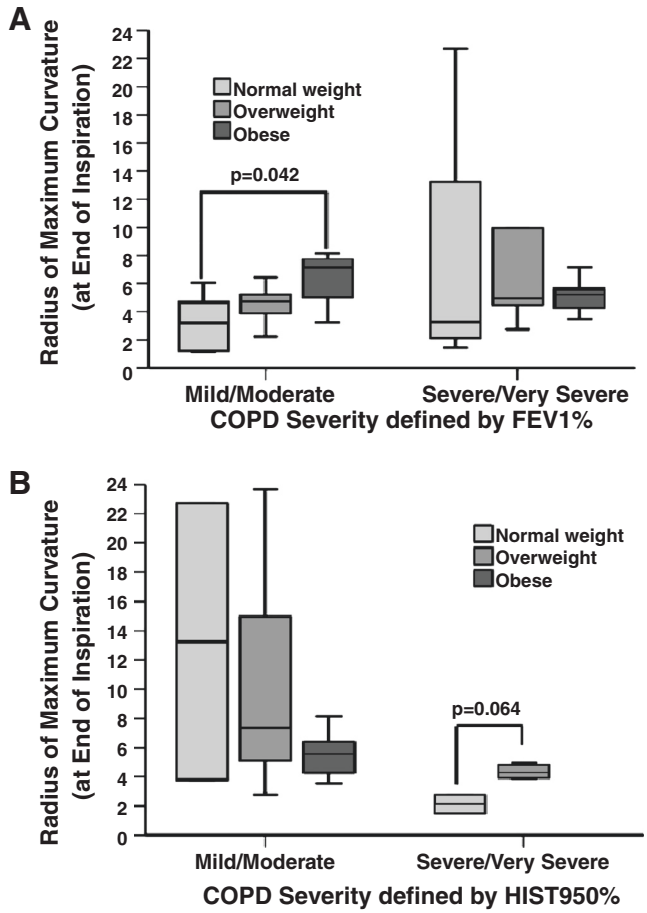

Fig. 4. *A*: box and whiskers plots of the R_{max} (in cm) at end of inspiration during quiet breathing in COPD subjects. Two groups of COPD subjects are shown: *1*) mild/moderate and *2*) severe/very severe subjects based on COPD severity define by forced expiratory volume (FEV)1%. An increasing trend in R_{max} with increase in BMI is observed in mild/moderate COPD group. R_{max} of the midcostal diaphragm is significantl greater in obese subjects than in normal weight subjects ($P = 0.042$). *B*: box and whiskers plots of the radius of maximum curvature R_{max} (in cm) at end of inspiration during quiet breathing in COPD subjects. Two groups of COPD subjects are shown: *1*) mild/moderate and *2*) severe/very severe subjects. Severity of the disease is based on COPD severity define by radiological assessment of emphysema (HIST950%). R_{max} in severe-to-very severe COPD subjects appears to increase with BMI, although the difference between overweight subjects and normal weight subjects did not reach significanc ($P = 0.064$).

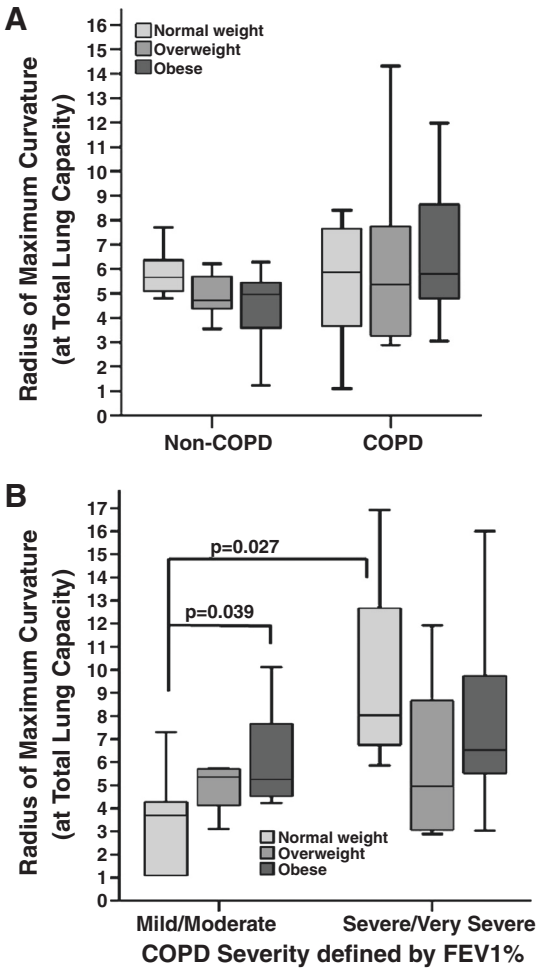

Fig. 5. *A*: box and whiskers plots of R_{max} (in cm) at total lung capacity in COPD subjects as well as smoker subjects with no history of lung disease are shown. There were no significan differences in R_{max} between the diaphragm in non-COPD and that in COPD subjects. *B*: box and whiskers plots of R_{max} (in cm) at total lung capacity in COPD subjects. Severity of disease was define by FEV1%. There is an increasing trend of R_{max} with BMI in mild/moderate subjects. More precisely, R_{max} is greater in obese subjects than in normal weight subjects in the mild/moderate disease group ($P = 0.039$). Also, increasing trend of R_{max} with COPD severity is also noticed in normal-weight subjects ($P = 0.027$). The severe/very severe subjects do not show a significan difference of R_{max} with BMI.

simpler version that was developed for the canine diaphragm to assess the relationship between muscle length and its curvature (4). The midcostal diaphragm is represented as a circular arc that begins from the CW to the central tendon. This model shows how the geometrical relationships of muscle fibe length and $R_{max,}$ as well as the size of its insertion on the chest wall, change with obesity and lung disease. In obese subjects, the R_{max} and the ring of diaphragm insertion on CW are larger than those in the normal-weight group for both COPD and non-COPD as depicted by our data. The model parameters used to generate Fig. 7 are summarized in Table 2.

DISCUSSION

In this study, we demonstrated that the shape of the diaphragm muscle and size of the ring of its insertion in non-COPD and COPD subjects are modulated by BMI. In particular, we showed that BMI modulates R_{max} in both smokers with no history of lung disease and in COPD subjects. In addition, we showed that R_{max} was larger in obese subjects in mild to moderate COPD subjects at both EI and TLC. This trend coincided with a significan increase in the size of ring of insertion in obese subjects in obese subjects with mild to moderate COPD. Our data suggested that BMI is a modulator of diaphragm shape, whereas comparing data for non-COPD with that of COPD subjects, COPD appears to have little effect on diaphragm shape as shown in Fig. 2*A*. Lack of significan difference between R_{max} in COPD subjects with R_{max} in non-COPD is probably related to the large variability in diaphragm shape in the COPD group. In addition, the lack of correlation between R_{max} in COPD subjects with measures of lung function such as FEV1 or FEV1/FVC (data not shown) is consistent with the observation that COPD had little effect on diaphragm shape.

In the classic and elegant model by Loring and Mead, the human diaphragm was conceptualized as a cylindrical zone of apposition with essentially no curvature in the axial direction, with a curved dome opposed to the lung (20). In contrast to Loring and Mead's model, our data in Fig. 1 of the diaphragm configuratio at TLC show that the midcostal region was approximately cylindrical but the axis of the cylinder was parallel to the line of insertion on the rib cage rather than paralleling the long axis of the body. This would indicate that the muscle fiber of the diaphragm are aligned with the direction of maximum curvature, and this is consistent with our results in the canine model (4, 5, 7, 13). This assumption is based on logical justificatio of maximizing the contribution of muscle contractile force to the pressure-generating capacity of diaphragm.

Previous studies provided evidence of reduced FRC in obese subjects (12, 15). Salome et al. suggested that the presence of adipose tissue around the rib cage, abdomen, and in the visceral cavity in obese subjects may cause an increased loading on the chest wall leading to a reduction in FRC (28). Those investigators also suggested that reduction of diaphragm downward movement due to increase in abdominal volume may likely be the cause of a decline in TLC in obese subjects (28). Consistent with these findings our data show that the size of diaphragm ring of insertion increases in the obese subject compared with normal-weight subjects, which is probably due to the increase in abdominal volume. This outward shift of the ring of insertion coincided with an increase in the R_{max} with BMI in non-COPD and mild/moderate COPD. A larger R_{max} in an obese subject would result in a reduced ability of its muscles to transmit tension into pressure as postulated by the Laplace Law (6).

It is well recognized that the structure and function of the diaphragm are affected during the course of COPD (17–19, 23, 24). Furthermore, other investigators suggested that inspiratory muscle weakness is associated with dyspnea and premature mortality in COPD (26, 29). Other studies also reported that in COPD the diaphragm muscles tend to remodel into fatigue-resistant phenotype muscle fibe (11, 18, 19, 23). Interestingly, other investigators reported that the diaphragm length and surface area were similar between those in normal subjects and those in COPD patients analyzed at similar absolute lung volume (8, 27, 31). In agreement with these data, results from the current study suggested that COPD severity may have

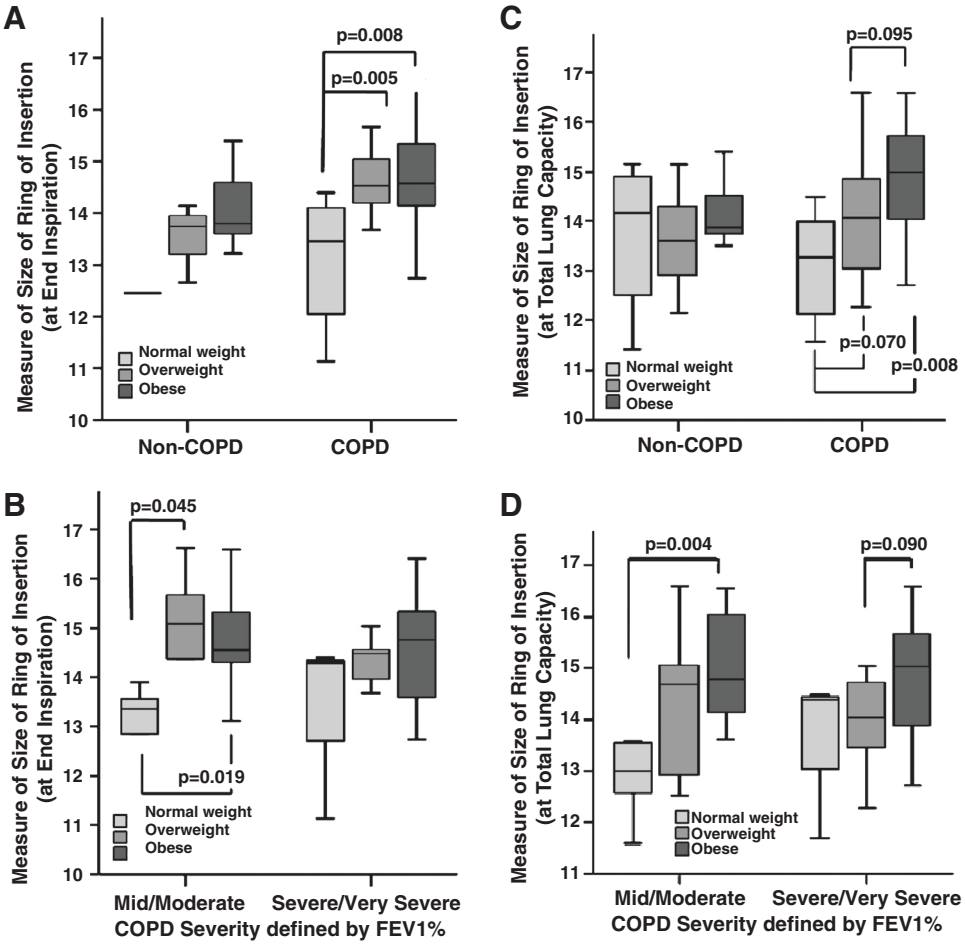

Fig. 6. *A*: box and whiskers plots of the size of diaphragm ring of insertion (in cm) at end of inspiration during quiet breathing in smoker subjects with no history of lung disease as well as COPD subjects. Size of ring of insertion of the diaphragm on chest wall insertion is not affected by BMI in non-COPD subjects. Size of ring of insertion increases significantl with BMI in COPD subjects with overweight ($P = 0.005$) and obese ($P = 0.008$) having larger size of ring of diaphragm insertion than those of normal weight. *B*: box and whiskers plots of the size of diaphragm ring of insertion (in cm) at end of inspiration during quiet breathing in COPD subjects. Two groups of COPD subjects are shown: *1*) mild/moderate and *2*) severe/very severe subjects based on COPD severity define by FEV1%. Size of ring of insertion significantl increases with BMI in mild/moderate subjects with overweight subjects ($P = 0.045$) and obese subjects ($P = 0.019$) having larger size of ring of insertion than normal-weight subjects. Size of ring of insertion does not show significan trend with BMI in severe/very severe COPD subjects. *C*: box and whiskers plots of the size of diaphragm ring of insertion (in cm) at total lung capacity during quiet breathing in COPD subjects as well as in smoker subjects with no history of lung disease. Size of ring of insertion does not show significan difference with BMI in non-COPD subjects. Size of ring of insertion significantl increases with BMI in COPD subjects with obese subjects ($P = 0.008$) having a larger size of ring of insertion than normal-weight subjects non-COPD. *D*: box and whiskers plots of the size of diaphragm ring of insertion (in cm) at total lung capacity during quiet breathing in COPD subjects. Two groups of COPD subjects are shown *1*) mild/moderate and *2*) severe/very severe subjects based on COPD severity define by FEV1%. Size of diaphragm ring of insertion significantl increases with BMI in mild/moderate subjects with obese subjects ($P = 0.004$) having a larger size of ring of insertion than normal-weight subjects. Size of ring of insertion appears to show an increasing trend with BMI in severe/very severe COPD subjects but the trend does not reach statistical significanc ($P = 0.09$).

minimal effect on R_{max} except in normal-weight subjects at TLC where severe/very severe subjects have significantl larger R_{max} than mild/moderate subjects. In addition, we found that there is a lack of correlation between R_{max} in COPD subjects with measures of lung hyperinflatio such as RV/TLC% and TLC predicted (data not shown). This is consistent with the observation that COPD had little effect on diaphragm shape. This suggests that the effect of disease severity on diaphragm configuratio is only pronounced at high lung volume and only in normal-weight subjects. Hence, our data suggest that COPD by itself may not be sufficien to signifi cantly alter diaphragm muscle curvature. In addition, disease severity does not appear to alter the size of diaphragm ring of insertion on the chest wall.

Although other investigators have made some progress in assessing the mechanical role of the diaphragm in subjects with COPD or emphysema (8, 10, 11), there has yet to be a satisfactory analysis of the shape and kinematics of diaphragm muscle fiber and chest wall insertion in those subjects. Other investigators reasoned that the presence of obesity in COPD may not be a disadvantage with respect to dyspnea because of the volume-reducing effects of obesity could potentially lead to mechanical and respiratory muscle function advantages (22). The balance between hyperinflatio effects of COPD with potential lung de-flatin effect of obesity may be important in determining the configuratio of the diaphragm particularly at low lung volumes. Our data in Fig. 2*B* are consistent with the hypothesis that BMI is a critical determinant of the configuratio of the diaphragm.

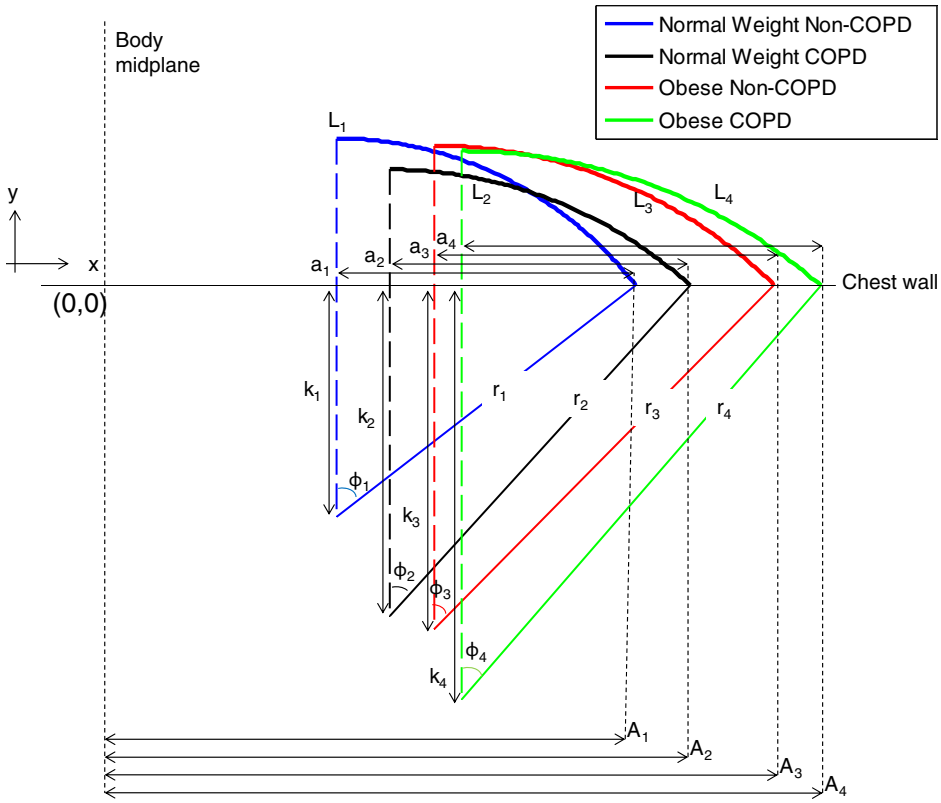

Fig. 7. Model describing the kinematics of the midcostal diaphragm in non-COPD and COPD for obese and normal-weight subjects taken at end inspiration. Model shows the effect of obesity on diaphragm radius of maximum curvature (r), midcostal hemidiaphragm length (L), and size of the ring of insertion (A) of the diaphragm on the chest wall (CW) shown in the plane of maximum curvature of the midcostal diaphragm. The body midplane was set as the reference point for the x-coordinate while the chest wall was set as the y-coordinate reference point (0, 0). In this model, the shape of the midcostal region of the diaphragm is pictured as being an arc of a circular cylinder that extends from the CW to the peak height of the diaphragm at distance (a). The center of the circular arc lies between the CW and the body midplane subtends an angle (φ). The x-coordinate for the arc center was set to be the difference of the ring of insertion, A, listed in Table 2 and distance a. The y-coordinate for the center (k) was determined from Pythagorean relation $\sqrt{r^2 - a^2}$. Hence, the coordinate of the arc center is (A-a, $-k$). The L and the r are related to a and φ by the following equations. $L = a\varphi/\sin\varphi$ (1); $r = a/\sin\varphi$ (2). The schematic above was generated using the average values of the parameters from our data calculated at end inspiration. Refer to Table 2 for a list of the parameters. Each subscript corresponds to each subject's group category in Table 2.

Data in Fig. 3 show that R_{max} was significantl increased in the obese COPD subjects compared with the normal-weight COPD subjects. Thus, these data may suggest that obesity is a negative regulator of diaphragm structure and consequently its function. Increasing abdominal fat would potentially displace the diaphragm cranially and the abdominal muscles outward and induce passive tension in both the abdominal and diaphragm muscles. This may cause an increase in abdominal elastance. Consequently, the volume displaced by the diaphragm in response to a given muscle activation may be reduced. It is possible that in obese subjects, diaphragm muscle fiber at FRC are longer and could develop greater force during muscle contraction.

Our data in Fig. 4*A* show that BMI modulated R_{max} in mild/moderate COPD obese subjects, while the trend was less apparent in severe/very severe COPD subjects. This may suggest that in severe/very severe COPD subjects, due to airflo limitation, the lungs are hyperinflated which could potentially balance the cranial displacement of the diaphragm caused by increased abdominal fat in obese COPD subjects, particularly in the supine position Other investigators showed that CT-quantifie emphysema distribution is associated with lung function decline (9). Interestingly, our data in Fig. 4*A* show contrasting effects of obesity on diaphragm configuratio in COPD subjects where the severity of disease is assessed by FEV1% when compared with those COPD subjects where severity of the disease is evaluated by radiological assessment of emphysema shown in Fig. 4*B*. Overall, the data in Fig. 4 are consistent with the postulate that the relationship between severity of COPD and R_{max} is affected by BMI. Furthermore, the approach of evaluating COPD severity, whether it is based on functional measurements of FEV1 or radiological assessment of emphysema, appears to be an important factor in determining such relationship. Curiously, our data showed that at a higher lung volume such as at TLC, the shape of the diaphragm was not altered with increased BMI in either non-COPD or COPD subjects as shown in Fig. 5*A*. Further analysis on COPD groups shown in Fig. 5*B* revealed potential shape

Table 2. *Summary of calculated parameters used to generate diaphragm model developed at lung volume of end of inspiration shown in Fig. 7*

Figure 7 Subscript Number	Subjects	r, cm	A, cm	a, cm	Φ, rad	k, cm	L, cm
1*	Normal weight Non-COPD	4.5	12.5	3.6	0.9	2.8	4.1
2	Normal weight All COPD	5.3 ± 3.2	13.1 ± 1.3	5.8 ± 0.9	1.0 ± 0.3	3.9 ± 3.1	7.3 ± 1.6
3	Obese Non-COPD	5.8 ± 1.3	14.1 ± 0.9	4.6 ± 0.3	0.9 ± 0.1	4.1 ± 1.0	5.3 ± 0.1
4	Obese all COPD	6.5 ± 2.7	14.7 ± 1.2	5.1 ± 1.3	0.8 ± 0.3	4.9 ± 3.4	5.4 ± 2.2

Summary of the calculated parameters (means ± SE) used to generate the diaphragm model developed at lung volume of end of inspiration shown in Fig. 7. Each parameter was averaged from each subject category. The diaphragm length (L) and radius of curvature (r) are related to peak diaphragm to chest wall (a) and angle span (φ) by the following equations. $L = a\varphi/\sin\varphi$ (1); $r = a/\sin\varphi$ (2). Horizontal distance between chest wall and center of curvature (k) was determined from Pythagorean relation, $\sqrt{r^2 - a^2}$. A, ring of insertion. *Data for $n = 1$.

dependency on BMI in mild/moderate ($P = 0.039$), whereas diaphragm shape at TLC in severe/very severe COPD subjects were not sensitive to BMI.

Our data revealed for the firs time, that BMI is an important determinant of the size of the ring of insertion in COPD at end of inspiration. Our data in Fig. 6*A* demonstrated a smaller ring of insertion in COPD subjects of normal weight compared with overweight COPD ($P = 0.005$) and obese COPD subjects ($P = 0.008$). Curiously, the size of ring of insertion is not sensitive to BMI in non-COPD subjects and severe/very severe COPD as demonstrated by the data shown in Fig. 6*B*. In contrast, the data in Fig. 6, *C* and *D*, are consistent with the postulate that BMI plays an important role in determining the size of diaphragm ring of insertion at total lung capacity, particularly in obese mild/moderate COPD subjects.

Our model in Fig. 7 shows that obesity displaces the diaphragm cranially and the chest wall outward in both non-COPD and COPD subjects, and this could be potentially due to the increase of abdominal fat. Our model in Fig. 7 provides a mechanism by which lung disease could only cause little change in the radius of maximum curvature by moving chest wall insertion outward and rotating muscle fiber around the insertion on the chest wall in the plane of its maximum curvature. This mechanism appears to be operable in the absence of obesity. However, our data show that obese COPD subjects show larger R_{max} compared with COPD subjects of normal weight. Consequently, the diaphragm in obese COPD subjects is anticipated to have lesser pressure-generating capacity compared with non-COPD subjects as postulated by Laplace Law (6). One of the limitations of this model is that it captures the kinematics of the diaphragm muscle fiber in the two-dimensional plane, whereas such kinematics could be three-dimensional and more complex. In particular, there is a potential of rotation of the muscle fibe out of its plane of maximum curvature, and such a rotation could affect the geometric relationships between R_{max} and size of diaphragm ring of insertion.

Our study provides insight regarding BMI influenc on both non-COPD and COPD subjects' adaptation of its respiratory mechanics via alteration of diaphragm shape especially at the EI during quiet breathing. Our study was limited, however, by a smaller number of subjects involved in the study, particularly, the normal weight non-COPD subjects, which may potentially reduce the statistical power of the study. Another potential limitation of our study is that our data on diaphragm shape were obtained in the supine posture where respiratory mechanics are different from that in the upright posture. In particular, during CT imaging in the supine position, abdominal contents could be shifted in a cephalad direction: a gravity-dependent effect that is in the opposite direction to the upright position. It is well known, however, that in the supine posture, the mechanical load on the diaphragm is increased in obesity (25), and therefore, there is a strong rationale for utilizing this posture in assessing obesity effects on diaphragm structure and chest wall kinematics. Curiously, our earlier published data in the canine model showed no dependency of diaphragm curvature on posture. More precisely, diaphragm muscle fibe curvature was similar in the midcostal region between supine and prone postures despite differences in gravitational forces between those two postures (5). Our study was also limited by the lack of measurements on subjects' abdominal circumferences and fat tissue distribution to accurately depict the extent of obesity and abdominal loading on the chest wall. However, a previous study confirme that BMI can adequately represent the magnitude of obesity since fat distribution is fairly similar in lean and obese subjects (2).

Perspectives and Significance

Our study demonstrates that BMI is an important determinant of diaphragm curvature, while COPD by itself does not appear to be associated with significan alteration in diaphragm shape. Our finding also demonstrate that BMI alters diaphragm curvature and size of its ring of insertion on the lower rib cage in non-COPD and COPD subjects. It is important to recognize that other investigators have shown that the presence of obesity in COPD does not represent a disadvantage with respect to dyspnea and exercise performance (22). Although the potential for lung-volume reducing effects of obesity on respiratory mechanics could explain the possibility of an advantage for respiratory muscle function (14), our data indicate the reduced curvature of the diaphragm muscle fiber in obese subjects may suggest that obesity provides a disadvantage rather than a benefi for respiratory muscle function in both non-COPD and COPD subjects. Our finding challenge the notion that obesity is beneficia for respiratory muscle mechanical function in COPD. Our results are consistent with *1*) the recent data by investigators of the COPDGene trial that support the hypothesis that obesity in subjects with COPD may contribute to a worse COPD-related course (16), as well as *2*) data from the ECLIPSE study showing more dyspnea and lower health status in obese COPD subjects (3) We propose that future research studies could be designed to *1*) uncover the causal mechanisms involved in altered respiratory system mechanics in obesity and *2*) unravel physiological mechanisms responsible of the role of obesity in modulating respiratory muscle function in COPD.

GRANTS

This project was funded by National Heart, Lung, and Blood Institute Grants NIH-RO1-HL072839 and NIH-R25-HL108853 and by a grant from the National Science Foundation.

DISCLOSURES

No conflict of interest, financia or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

A.M.B., E.A.H., and A.S. conceived and designed research; A.M.B., M.A.L., C.V., and A.S. performed experiments; A.M.B., C.V., A.F., and S.W. analyzed data; A.M.B., C.V., A.F., and T.G.B. interpreted results of experiments; A.M.B. drafted manuscript; A.M.B., A.A.B., S.W., T.G.B., and N.A.H. edited and revised manuscript; A.M.B., M.A.L., C.V., A.A.B., A.F., S.W., T.G.B., N.A.H., E.A.H., and A.S. approved fina version of manuscript; C.V., A.A.B., A.F., and S.W. prepared figures

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