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대한영상의학회지

Quantitative Computed Tomography Assessment of Respiratory Muscles in Male Patients Diagnosed with Emphysema
폐기종 환자에서 호흡 근육의 양적 CT 평가

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Purpose: The aim of this study was to accurately evaluate the significance and correlation between the clinical severity and the morphologic feature of respiratory muscles in patients with emphysema as noted using computed tomography (CT).
Materials and Methods: The cross sectional area (CSA) and attenuation of respiratory muscles in the patients with emphysema (n = 71) were subsequently retrospectively reviewed. The clinical severity for the patients was determined by the value of the actual forced expiratory volume in 1 second/forced vital capacity at the pulmonary function test (PFT). The correlation between the CT measurements with visual assessment of emphysema (VAE), and the PFT values were completed and recorded. The multiple linear regression analysis of each CT measurement on the VAE and PFT values was used to determine the most affective parameters among the recorded and identified CT measurements.
Results: The CSA of the pectoralis major (p = 0.002) and subsequently the serratus anterior (p = 0.011) were found to be lower in patients with emphysema than as compared to those in the control group. The CSA and the attenuation of respiratory muscles remained significant for its relation for the VAE and PFT values. As noted, both the VAE and PFT values were mostly contributed by the CSA and attenuation of serratus anterior and attenuation of diaphragm crus among all respiratory muscles.
Conclusion: The CT measurement of the patient's respiratory muscles may reflect clinical and visual severity in the patients with emphysema.

Index terms
Pulmonary Disease, Chronic Obstructive
Emphysema
Multidetector Computed Tomography
Respiratory Muscles
Diaphragm

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INTRODUCTION

Respiratory muscles in the patients with chronic obstructive pulmonary disease (COPD) are affected structurally and physiologically in complex way. Research on respiratory muscles in patients with COPD and physiopathological effects on their performances basis has been performed in the past, but they have shown no gross morphologic changes of the muscles (1-8). A few studies in particular measured the apposition length of diaphragm at the costal insertion either indirectly by a chest radiograph or by spiral computed tomography (CT) in the patients with COPD. With arising interest on functional impairment of COPD, a few recent studies focused on showing clinical correlation of the cross sectional areas of pectoralis muscle, intercostals and latissimus dorsi muscle (9, 10) visualized at chest CT in COPD patients. Although these investigations provided compelling data for functional correlation of each respiratory muscle, they limited to analyze one or two respiratory muscles at a time.

CT emphysema or ventilation quantification has already demonstrated a good correlation with clinical severity (11, 12). Visual assessment of emphysema by using standard CT image was proven to be simple and reliable. To improve practical applicability we used visual assessment of emphysema at standard

CT image. We analyzed several respiratory muscles in thoracic cavity to find the most effective muscle which correlates well with pulmonary function test and visual assessment of emphysema. Cross sectional area and attenuation of respiratory muscles were analyzed to evaluate the changes of muscle mass and fat infiltration in the patients with emphysema. The aim of this study was to establish the correlation of respiratory muscle with clinical and visual severity of emphysema visualized at CT.

MATERIALS AND METHODS

Patient and Control Selection

The Institutional Review Board (IRB No. 13-151) of our institution approved this retrospective study and the need for an informed consent was waived. Using a computerized search of the radiology database, we retrospectively found 545 male patients with "confluent centrilobular emphysema," "advanced destructive emphysema," or "panlobular emphysema" at chest CT reading at our university hospital from April 2011 to November 2013. Although dominant centrilobular emphysema with mild paraseptal emphysema were included, paraseptal emphysema only cases were not included as these cases are known of little physiologic significance, compared with centrilobular or panlobular emphysema which are associated with increased symptoms and reduced exercise capacity (13, 14). Exclusion criteria of the study were as follows: 1) The patients who had undergone low dose CT scan (n = 75) as attenuation obtained at low dose CT scans are easily affected by streak artifact from adjacent bony thorax (15). 2) Female patient to remove gender difference in muscle thickness (16). 3) The patients with other chronic systemic or pulmonary disease, those with known malignancy and those with chest trauma which may affect form of thoracic cavity. Of the remaining 117 patients, only 71 patients had undergone a pulmonary function test within one month from the time when chest CT was performed. The control group was composed of 24 healthy male subjects who were age and body mass index (BMI) matched and received both a chest CT and an abdominal CT with the tests within one month of each other.

Spirometry Procedure and Analysis

Pulmonary function test (PFT) with spirometry was performed on a body plethysmograph connected to a computer for data analysis (Vmax 22 and 6200, Sensormedics, Yorba Linda, CA, USA). The two values from the spirometry reports were the actual forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) and the % of predicted FEV_1. The obstructive impairment of the patients was staged according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria. Patients were staged according to the spirometry results as having normal airway function (FEV_1/FVC ≥ 0.7), mild obstruction (FEV_1/FVC < 0.7 and FEV_1 ≥ 80% predicted), moderate obstruction (FEV_1/FVC < 0.7 and FEV_1 ≥ 50% but < 80% predicted), severe obstruction (FEV_1/FVC < 0.7 and FEV_1 ≥ 30% but < 50% predicted) and very severe obstruction (FEV_1/FVC < 0.7 and FEV_1 < 30% predicted).

CT Technique

A 320-channel, 64-channel, or 16-channel multi detector CT were performed on different scanners (Aquilion ONE, Toshiba, Otawara, Japan; SOMATOM Definition and Sensation 16, Siemens Medical Systems, Forchheim, Germany; Optima CT 660, GE Medical Systems, Milwaukee, WI, USA). Chest CT scans with contrast enhancement were performed, using the following scan parameters: 0.6–1.2 collimation, 120 kVp; 100–250 mA under automatic exposure control and 0.5–0.75 seconds rotation time. CT scans were reconstructed at section widths of 2.5 mm. Subjects were routinely asked to breathe in to functional residual capacity and to hold their breath to take chest CT scan.

Assessment and Measurements

Pectoralis major, pectoralis minor, intercostalis, serratus anterior, latissimus dorsi, and diaphragm were measured at different scan levels. We used diaphragm crura for direct measurement, while previous studies used the costal diaphragm with indirect estimation at radiograph (17-19). Following level of measurement was determined when respiratory muscles were entirely visualized with the largest area and clearly differentiated with each other. Our six measurements were as follows (Fig. 1): 1) pectoralis major: at the level of claviculomanubrial joint, on axial scan, 2) pectoralis minor: the same way as pectoralis major muscle, on axial scan, 3) intercostalis: measurement from the innermost intercostal to the external intercostal including intercostal fat at the level of right inferior pulmonary vein into

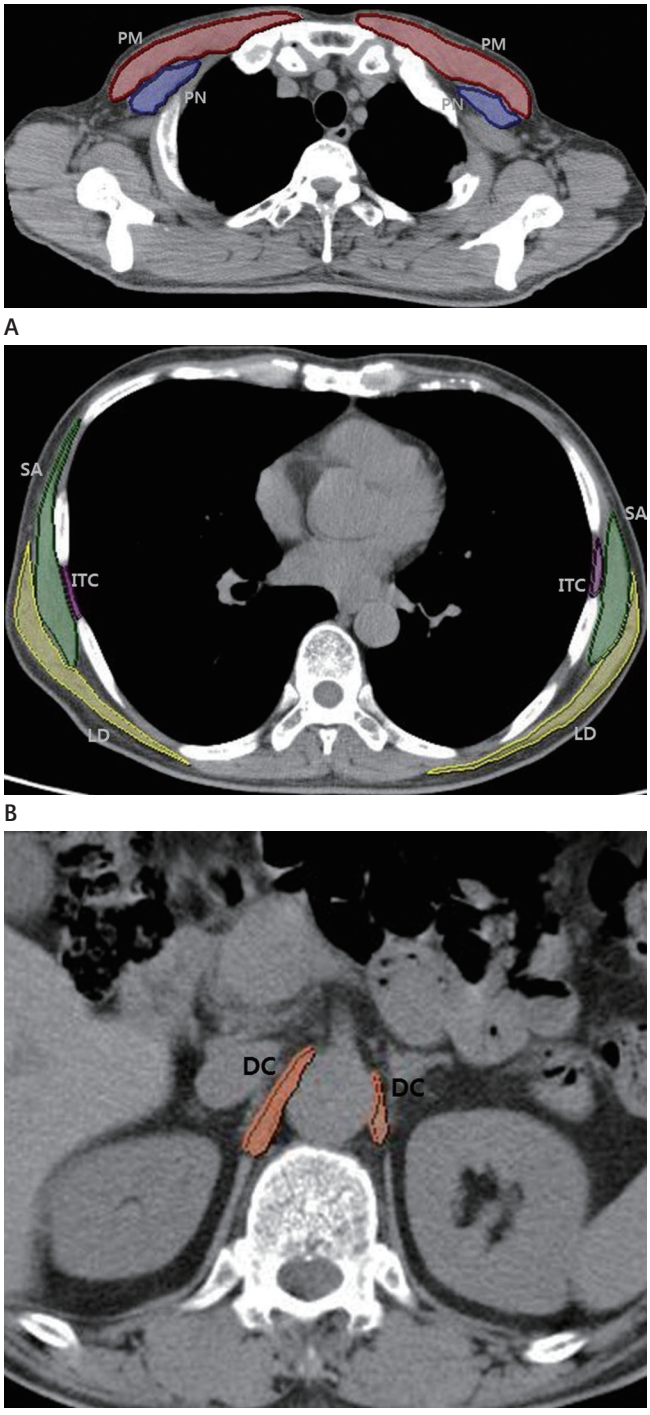

Fig. 1. Sample CT scans used to measure cross sectional area of respiratory muscles.
A. The cross sectional area of PM (red) and PN (blue) are measured at the level of the claviculomanubrial joint.
B. The cross sectional area of ITC (purple), SA (green), and LD (yellow) are measured at the level of right inferior pulmonary vein.
C. The cross sectional area of DC (orange) is measured at the retrocrural area at the level of origin of the celiac trunk.
DC = diaphragm crus, ITC = intercostalis, LD = latissimus dorsi, PM = pectoralis major, PN = pectoralis minor, SA = serratus anterior

left atrium, on axial scan, 4) serratus anterior: at the same level of right inferior pulmonary vein into left atrium, on axial scan, 5) latissimus dorsi: at the level of right inferior pulmonary vein into left atrium, on axial scan, and 6) diaphragm crus: measurement of the crus in the retrocaval area at the level of the origin of the celiac trunk, on axial scan.

We manually drew the region of interest (ROI) of the outermost border of each muscle where the muscle was well-delineated by surrounding fat. Mean area and mean attenuation of within ROI were calculated automatically. Drawing the ROI was taken at both sides of the muscle. Mean areas of the respiratory muscles were summed as cross-sectional area (CSA). Mean attenuation was calculated by averaging both sides of attenuation. The measurements were taken at the given level 5–7 millimeters above when the measurements became unavailable: when the margin of the muscle was vague without surrounding fat due to severe weight loss (n = 3), when the muscle was not fully covered on CT scan (n = 2).

The visual assessment of emphysema severity was designated as visual assessment of emphysema (VAE) based on the method suggested by Kim et al. (20). The extent of emphysema in each lobe was also assessed by using a six-point scale system: 0, 1–5, 6–25, 26–50, 51–75, and greater than 75%. The lingula was considered a different lobe, resulting in six lobes for each case. The visual extent of emphysema for the whole lung was calculated by adding the six-point scale scores in six lobes. The CT images were visually inspected at constant window width of 1500 Hounsfield unit (HU) and a window level of -700 HU.

All images were assessed by two different readers to account for the interobserver variability. Readers were chest radiologists with 3 and 4 years of experience, respectively. The readers were blinded to patient clinical data and results from the other reader. We re-analyzed the entire patient data after a period of 1 month to determine intraobserver variability. Finally datas of two readers were averaged for statistical analysis.

Statistical Analysis

The interobserver and intraobserver variability was evaluated by using intraclass correlation coefficients with two-way mixed absolute model. The statistically significant difference between the patient with emphysema and control group was analyzed with a Student t test for the normally distributed parameters

and with the Mann-Whitney U test for parameters that were not normally distributed. Pearson correlation coefficient were performed to evaluate the relationships between the CT measurements with VAE and FEV_1/FVC. Linear regression analysis was performed to adjust confounders including age and BMI for CSA and attenuation of respiratory muscles. Stepwise linear regression analysis was performed to determine the most affective parameters of VAE and FEV_1/FVC among CSA measurements. All CSAs of respiratory muscles were included as independent variables. The relationship between mean attenuations and VAE stage and FEV_1/FVC were also performed. All mean attenuations of respiratory muscles were included as independent variables. Statistical significance was considered when $p < 0.05$. SPSS software (Version 20.0, IBM Corp., Armonk, NY, USA) was used for statistical evaluations.

RESULTS

Characteristics of patients with emphysema are summarized in Table 1. The CSA of respiratory muscles were found to be lower in patient with emphysema than in the control group. Significant differences in measurements of CSA were found between the patients with emphysema and controls in terms of the pectoralis major, serratus anterior by using Student *t* and Mann-Whitney U test (Table 2). Attenuation of respiratory muscles was lower in the patients with emphysema, but that was not statistically significant (Table 2). Interobserver and intraobserver agreement throughout all CT measurements was good and with substantial agreement (Table 3).

Correlations of CT measurements and clinical, visual stage of emphysema are shown in Table 4. Overall, VAE was correlated with eight parameters of all CT measurements. Their correlation coefficient ranged from -0.245 to -0.408. FEV_1/FVC was correlated with five parameters of all CT measurements. Their correlation coeffiecient ranged from -0.270 to -0.390. VAE

Table 1. Characteristics of 71 Male Patients with Emphysema

Total patient number	71
Age (years)	69.6 ± 10.2
BMI (kg/m^2)	21.7 ± 3.3
GOLD stage	
Normal	12
Mild	14
Moderate	16
Severe	22
Very severe	7
VAE*	
0% (6 point)	0
1–5% (7–11 point)	1
6–25% (12–17 point)	17
26–50% (18–23 point)	37
51–75% (24–29 point)	14
> 75% (30–36 point)	2

Data are presented as mean ± standard deviation.
*The visual extent of emphysema for the whole lung was expressed by averaging the sum of six-point scale scores of six lobes.
BMI = body mass index, GOLD = Global Initiative for Obstructive Lung Disease, VAE = visual assessment of emphysema

Table 2. CT Measurements of Respiratory Muscles

	Emphysema (*n* = 71)	Control (*n* = 24)	*p*-Value
Age (years)	69.6 ± 10.2	68.8 ± 13.3	0.249
BMI (kg/m^2)	21.7 ± 3.3	20.5 ± 3.3	0.383
Height (m)	1.66 ± 0.06	1.69 ± 0.07	0.108*
CSA (cm^2)			
Pectoralis major	21.9 ± 5.9	26.5 ± 6.8	0.002*
Pectoralis minor	7.7 ± 2.1	7.9 ± 2.2	0.566
Intercostal	1.0 (0.2–3.2)	0.8 (0.3–2.3)	0.155†
Serratus anterior	12.1 ± 5.0	15.4 ± 5.8	0.011*
Latissimus dorsi	11.7 (3.1–23.6)	13.0 (6.0–24.7)	0.136†
Diaphragm crus	2.7 ± 1.0	2.8 ± 1.3	0.644
Attenuation			
Pectoralis major	47.4 ± 10.3	45.1 ± 8.0	0.736
Pectoralis minor	45.9 ± 8.6	44.4 ± 6.4	0.149
Intercostal	2.3 ± 14.7	2.6 ± 17.4	0.320
Serratus anterior	39.8 (9.5–59.8)	42.3 (25.5–59)	0.300†
Latissimus dorsi	27.0 (-14.5–52.5)	31.0 (-0.2–51.5)	0.222†
Diaphragm crus	32.2 ± 10.6	35.8 ± 7.8	0.138

Data are presented as mean ± standard deviation.
*Significative *p*-values.
†If Mann-Whitney U test was performed, data were presented as median with range in parentheses.
BMI = body mass index, CSA = cross sectional area

Table 3. Repeatability of CT Measurements of Respiratory Muscles

Respiratory Muscles	Intraclass Correlation Coefficient			
	Intraobserver		Interobserver	
	CSA	Attenuation	CSA	Attenuation
Pectoralis major	0.853	0.900	0.713	0.853
Pectoralis minor	0.822	0.811	0.795	0.781
Intercostalis	0.751	0.852	0.651	0.809
Serratus anterior	0.944	0.882	0.929	0.823
Latissimus dorsi	0.867	0.913	0.848	0.901
Diaphragm crus	0.732	0.683	0.683	0.683

CSA = cross sectional area

showed correlation with clinical traits, including FEV_1/FVC (r = -0.604, $p < 0.001$) and BMI (r = -0.232, $p = 0.051$).

Linear regression models of CT measurements with VAE adjusted for BMI and age are shown in Table 5. CT measurements of serratus anterior consistently showed correlation with clinical and visual severity of emphysema, when BMI and age were controlled. Lastly, stepwise multiple linear regression analysis was performed to evaluate the CT parameter with the highest impact on VAE and FEV_1/FVC. VAE was most contributed by CSA of serratus anterior ($p = 0.001$), when CSA of all respiratory muscles were included as independent variables ($R^2 = 0.151$, $p = 0.001$). FEV_1/FVC was mostly contributed by CSA of Serratus anterior ($p < 0.001$) with the same variables ($R^2 = 0.175$, $p < 0.001$). Among attenuation measurements, VAE was most contributed by diaphragm crus ($p = 0.012$), pectoralis minor ($p = 0.014$) and serratus anterior ($p = 0.046$) ($R^2 = 0.302$, $p < 0.001$). GOLD stage was most contributed by diaphragm crus ($p = 0.012$) and attenuation of serratus anterior ($p = 0.040$) ($R^2 = 0.198$, $p = 0.001$). Overall, VAE and FEV_1/FVC consistently contributed by CSA and attenuation of serratus anterior, and attenuation of diaphragm crus. The distribution of CSA and attenuation of serratus anterior according to VAE and FEV_1/FVC is shown in Fig. 2.

Table 4. Pearson Correlation Coefficient (r) between CT Measurements and FEV_1/FVC

Variables	VAE (p-Value)	FEV_1/FVC (p-Value)
CSA		
Pectoralis major	-0.210 (0.078)	-0.052 (0.227)
Pectoralis minor	-0.144 (0.232)	-0.105 (0.904)
Intercostalis	-0.245 (0.040)*	-0.064 (0.613)
Serratus anterior	-0.389 (0.001)*	-0.390 (0.001)*
Latissimus dorsi	-0.343 (0.003)*	-0.285 (0.022)*
Diaphragm crus	-0.138 (0.250)	-0.083 (0.513)
Attenuation		
Pectoralis major	-0.330 (0.005)	0.207 (0.098)
Pectoralis minor	-0.408 (< 0.001)*	0.271 (0.029)*
Intercostalis	-0.328 (0.005)*	0.210 (0.094)
Serratus anterior	-0.376 (0.001)*	0.334 (0.007)*
Latissimus dorsi	-0.138 (0.251)	0.155 (0.217)
Diaphragm crus	-0.329 (0.005)*	0.376 (0.002)*

*Correlation coefficient with significative p-values.
CSA = cross sectional area, FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity, VAE = visual assessment of emphysema

DISCUSSION

We demonstrated that CSA and attenuation of respiratory muscles correlated with clinical and visual severity of COPD. CSA and attenuation of serratus anterior were consistently correlated both with clinical and visual severity of emphysema.

Interobserver and intraobserver variability showed substantial agreement in CT measurements in the present study. CSA and attenuation of intercostalis showed moderate agreement and severe variation in attenuation measurements due to inaccuracy of manual measurement in thin muscle. A previous study had shown good correlation between measurements of intercostal muscle and COPD severity, using CT histogram; in that

Table 5. Relationship of CT Measurements of Respiratory Muscles to VAE and FEV_1/FVC in Patients with Emphysema, Respectively

Respiratory Muscles	VAE				FEV_1/FVC			
	CSA		Attenuation		CSA		Attenuation	
	β	p-Value	β	p-Value	β	p-Value	β	p-Value
Simple regression								
Pectoralis major	-0.202 cm^2	0.247	-0.130	0.007*	0.229 cm^2	0.629	0.256	0.238
Pectoralis minor	-0.048 cm^2	0.863	-0.192	0.001*	-0.408 cm^2	0.736	0.428	0.083
Intercostalis	-1.197 cm^2	0.220	-0.092	0.004*	0.911 cm^2	0.836	0.211	0.142
Serratus anterior	-0.333 cm^2	0.004*	-0.172	< 0.001*	1.444 cm^2	0.004*	0.524	0.013*
Latissimus dorsi	-0.321 cm^2	0.026*	-0.044	0.195	1.262 cm^2	0.047*	0.134	0.360
Diaphragm crus	-0.154 cm^2	0.770	-0.115	0.014*	0.661 cm^2	0.771	0.551	0.007*
Stepwise multiple regression								
Serratus anterior	-0.312 cm^2	0.001*	-0.122	0.046*	1.760 cm^2	< 0.001*	0.419	0.040*
Diaphragm crus	-	-	-0.111	0.012*	-	-	0.492	0.012*
Pectoralis minor	-	-	-0.164	0.014*	-	-	-	-

*Significative p-values.
CSA = cross sectional area, FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity, VAE = visual assessment of emphysema

study, bilateral twelve intercostals muscles have been evaluated (10). Sum of total areas would be more reliable in the case of intercostals muscles according to the result of our and previous study.

Our study showed that the CSA of pectoralis major, serratus anterior is significantly lower in patients with emphysema than those in healthy controls. Previous studies have revealed that 4–35% of COPD patients had reduced skeletal muscle mass which included lower limb. This was explained by an up-regulation of protein degradation at the cellular level as in chronic and inflammatory conditions (21-24). In our study, attenuation of respiratory muscles was lower in patients with emphysema without statistical significance. As the thickness and area of respiratory muscles are smaller in emphysema group, there might be attenuation artifact from attached sternum or ribs.

Measurement of CSA might be reliable indicator correlating muscle atrophy or loss of fat free mass. Previous studies found that cross sectional area of quadriceps muscles fiber reduced in cellular level (22). Further, gross area of pectoralis muscle correlated with fat-free mass in another study (9). We presumed the decrease of CSA and attenuation might reflect muscle atrophy.

In the present study, CSA and attenuation of respiratory mus-

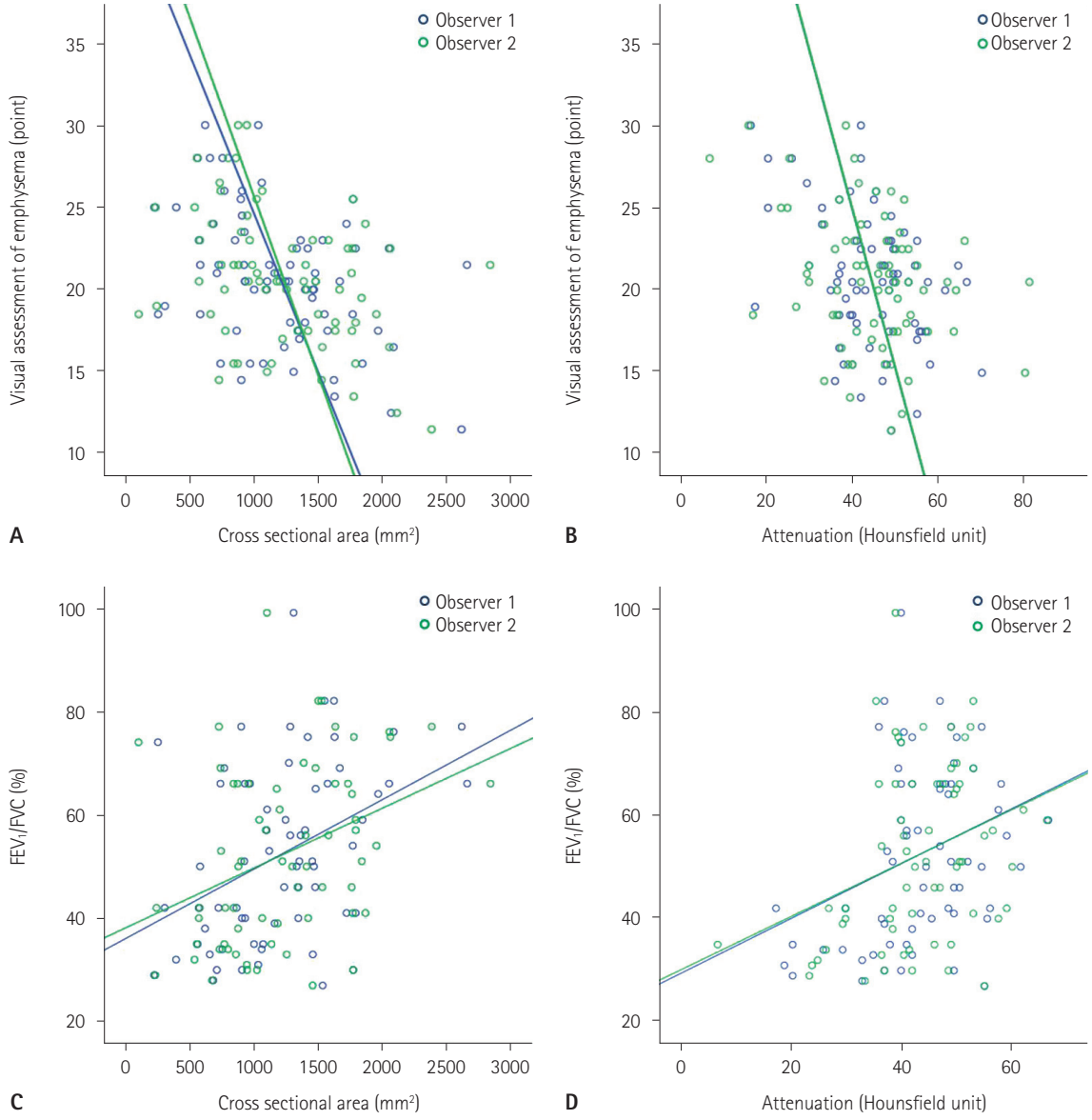

Fig. 2. Correlation of CT measurements of serratus anterior according to visual assessment of emphysema **(A, B)** and FEV_1/FVC **(C, D)**.
FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity

cles were associated with the result of PFT and visual extent of emphysema. These results are consistent with prior studies of quantitative CT measures of respiratory muscles in COPD patients (10, 22). In previous studies the area of pectoralis or latissimus dorsi muscles showed correlation with the COPD severity (9, 10). In our study the area of pectoralis muscles weren't statistically significant in the correlation with the results of PFT. Among many respiratory muscles, we hypothesized that serratus anterior muscles can be less affected by one's exercise or right or left handedness (25). Although many respiratory muscles correlated with clinical and visual extent of emphysema, we suggest that the area and attenuation of serratus anterior muscle maybe helpful to correlate both with emphysema extent and the result of PFT.

Certain limitations of this study need to be considered. First, there are locational variations of respiratory muscles in each subjects to measure cross sectional area at the same level uniformly. The fixed slice was selected because it was easily identifiable and could be replicated. Second, as patients with centrilobular or panlobular emphysema were included in this study, paraseptal emphysema was not included in the study. Another limitation of our study is its relatively small number of patients and its retrospective nature. Although we adjusted age, gender, BMI, other confounding factors such as exercise capacity, smoking history, prolonged administration of steroid may affect the body mass of subjects. We performed an analysis of the respiratory muscles in a single axial slice through the chest. Assessing muscle area on multiple slices or volume measurement would be accurate. However measurement of many respiratory muscles might lack clinical applicability in daily practice. Further, manual measurements might be inaccessible, as shown in wide variation in measurement of intercostalis muscle indices. Although visual assessment of emphysema showed good correlation with CT measurements of respiratory muscles, functional analysis of emphysema extent by postprocessing software would be preferable to improve accuracy (26).

In this study, we found that CT measurements of respiratory muscles in patients with emphysema had the correlation with the clinical and visual severity of emphysema. This may provide the ancillary information in evaluating the severity of emphysema.

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폐기종 환자에서 호흡 근육의 양적 CT 평가

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목적: 이 연구의 목적은 폐기종 환자에서 임상적 중증도와 CT를 이용한 호흡근육의 형태학적인 변화와의 상관관계를 평가하기 위함이다.

대상과 방법: 71명의 폐기종 환자에서 CT에서 측정한 호흡 근육의 단면적과 감쇠 계수를 후향적으로 평가하여 폐기종 환자와 24명의 대조군과의 차이점을 분석하였다. 임상적 중증도는 폐 기능 검사의 actual forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) 값으로 정의하였다. 폐기종의 시각적 평가 및 폐 기능 검사와 CT 측정치의 상관관계를 분석하고, CT 측정치 중에 가장 영향력 있는 변수를 알기 위해 폐기종의 시각적 평가와 폐 기능 검사에 대한 각 CT 측정치의 다중선형회귀 분석을 실시하였다.

결과: 폐기종 환자에서 큰가슴근 (p = 0.002), 앞톱니근 (p = 0.011)의 단면적이 대조군과 비교하여 작았다. 신체 비만계수와 나이를 통제하였을 때, 호흡 근육의 단면적과 감쇠 계수는 폐기종의 시각적 평가와 폐 기능 검사와 유의한 관계를 보였다. 폐 기종의 시각적 평가와 폐기능 검사는 모든 호흡근 중 앞톱니근의 단면적 및 감쇠 계수와 가로막 다리의 감쇠 계수에 가장 큰 영향을 받았다.

결론: 호흡 근육의 CT 측정치는 폐기종 환자의 임상적, 시각적인 중증도를 반영할 수 있다.

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