Relationship between Emphysema Quantification and COPD Severity

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Objective: *To determine the association between emphysema extent from high-resolution computed tomography (HRCT) and the physiological derangement in patients with chronic obstructive pulmonary disease (COPD).*
Material and Method: *A cross-sectional study was undertaken to quantify the emphysema severity in 23 COPD patients by automated HRCT scoring techniques. Correlation with phenotypic characters in term of exercise capacity [Modified Medical Research Council (mMRC) dyspnea scale, and 6-minute walk distance (6MWD)], pulmonary function testing [spirometry (forced expiratory volume in 1 second, FEV_1 and forced vital capacity, FVC), and diffusing capacity (DLCO)], were then assessed.*
Results: *Nineteen patients were male and four were female, the mean age was 73±8 years, with the mean FEV_1 %predicted of 67.8±25.4. Percentage of inspiratory emphysematous lung volume (%ELVi) had significant negative correlation with %FEV_1/FVC ($r = -0.50$, $p = 0.016$) and DLCO ($r = 0.58$, $p = 0.011$). Percentage of expiratory emphysematous lung volumes (%ELVe) also had the same correlation with %FEV_1/FVC ($r = -0.58$, $p = 0.004$) and DLCO ($r = 0.48$, $p = 0.042$). In addition, %ELVe also had significant negative correlation with 6MWD ($r = 0.50$, $p = 0.016$), but had significant positive correlation with mMRC scale ($r = 0.53$, $p = 0.01$).*
Conclusion: *Severity of emphysema assessed by HRCT was well correlated with pulmonary function test results and exercise capacity. It can be used as one aspect of phenotypic characters in patients with COPD, for designing personalize management plan.*

Keywords: *Emphysema quantification, COPD phenotype*

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Chronic obstructive pulmonary disease (COPD) is one of the major burdens to human health worldwide. Emphysema, an essential structural abnormality in patients with COPD, is defined as abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of alveolar walls, without obvious fibrosis(1). Only when the lungs are severely affected by emphysema, do symptoms set in, and few treatment options exist. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), multifacet assessment including symptoms, spirometry, exacerbation risks, and co-morbidities, may enhance a tailor-made management plan for an individual patient(2).

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Computed tomography (CT) has been used widely for in vivo analysis of pulmonary emphysema on the basis of morphometric demonstration. With the advent of high-resolution CT scan (HRCT), quantification of emphysema with well histopathological correlation was clearly established(3-8). In addition, CT is more sensitive and more specific than pulmonary function testing for the diagnosis of emphysema, and may be superior to the declining of forced expiratory volume in 1 second (FEV_1) for the evaluation of emphysema progression in patients with alpha-1 antitrypsin deficiency(9).

Conventionally, emphysema quantification was performed using subjective grading based on visual analysis or objective semiautomatic techniques based on tissue density, such as a density mask(5). The incorporation of helical technique for including the whole lung volume, instead of using discrete noncontiguous axial images, has been shown to have more accuracy in quantification process(10,11). Volumetric quantification based on CT densitometry (CT densitovolumetry) is a technique that uses post-processing tools applied to data acquired by helical CT, for measuring volumes of zones with different densities. If performed in inspiration and expiration, it can provide both static and functional information about the lungs such as total lung volume in both states, that is, fully expanded and fully contracted, and therefore, the shrinking capacity of the lungs. Shrinking capacity means the capacity to expel part of the contained air and blood from the lungs, as well as the degree of compressibility of the lungs by the thoracic cage and diaphragm.

This cross-sectional study aims to examine the relationship between radiologic extent of emphysema, and the physiologic derangement from pulmonary function testing and exercise capacity. The greater extent of HRCT-defined emphysema is hypothesized to determine more severe physiological impairment and lower exercise capacity in patients with COPD.

Material and Method

Patients in COPD Clinic of Siriraj Hospital who had HRCT performing as part of an evaluation of co-morbidities were recruited. Pulmonary function testing and six minute walk test results within 12 months apart from HRCT were also selected for the study. Sample size was calculated to be 23 patients on the assumption of correlation coefficient between HRCT and FEV_1 is -0.62 from previous study[12], with standard normal of 1.96 and statistical significant value of 5% and power of 90%. Demographic data, Modified Medical Research Council (mMRC) dyspnea scale, and BODE index (body mass index, airflow obstruction, dyspnea, exercise performance), were extracted from medical records. The study was approved by the Institutional Ethics Committee.

Spirometry, lung volume assessed by body phlethysmography or nitrogen wash-out method, diffusing capacity, and 6-minute walk test, were measured with the techniques which comply with the American Thoracic Society recommendation. The absolute and predicted values of FEV_1, forced vital capacity (FVC), inspiratory capacity (IC), total lung capacity (TLC), diffusing capacity to carbon monoxide (DLCO), and 6-minute walk distance (6MWD) were recorded.

HRCT was performed by non-contrast, 2 dimensions, 64 slides, 120 kV, 50 mA, 0.625 mm intervals from the apex of the lung to the diaphragm using a software (Alatoview, Toshiba, Japan). The threshold of -950 HU was selected, and software for emphysema scoring (Thoracic VCAR HD, Avantage Workstation version, GE Medical system, USA) was used for automatic segmentation of the lungs without inclusion of central airways. A second segmentation was then performed based on a density band to subdivide the total lung volume into normal lung volume, which included all voxels with densities between -950 and -250 HU, and emphysematous lung volume, which included only voxels with densities below -950 HU. The same process was also applied for the images acquired in expiration, which derived in various parameters (Table 1).

Data are presented as means ± SD. The SPSS 16.0 software package was used for statistical analyses, and a p-value <0.05 was considered statistically significant. Pearson and Spearman's correlation analyses were used to determine the correlations between the studied parameters.

Results

Among 23 patients with COPD, 19 were male and 4 were female. Others demographic, physiologic, radiographic, and clinical data are listed in Table 2.

Table 1. Variables and descriptions used for emphysema quantification

Variable	Description
Inspiratory total lung volume (TLVi)	Voxels with densities below -250 HU, measured at total lung capacity (TLC)
Expiratory total lung volume (TLVe)	Voxels with densities below -250 HU, measured at residual volume (RV)
Inspiratory normal lung volume (NLVi)	Voxels with densities between -950 and-250 HU, measured at TLC
Expiratory normal lung volume (NLVe)	Voxels with densities between -950 and -250 HU, measured at RV
Inspiratory emphysematous lung volume (ELVi)	Voxels with densities below -950 HU, measured at TLC
Expiratory emphysematous lung volume (ELVe)	Voxels with densities below -950 HU, measured at RV
% inspiratory emphysematous lung volume (%ELVi)	ELVi/TLVi x100
% expiratory emphysematous lung volume (%ELVe)	ELVe/TLVe x100

The median interval between CT and pulmonary function testing was 1-6 months, 5 patients could not perform diffusing capacity and lung volume measurements.

Significant negative correlation between both %FEV_1/FVC and DLCO %predicted with %ELVi and %ELVe were observed. In addition, %ELVe was also inversely correlated with %IC/TLC. Both %ELVi and %ELVe had significant positive correlation with BODE index. Only %ELVe had significant positive correlation with MMRC and negative correlation with 6MWD (Table 3, 4).

Discussion

COPD is a well-recognized disease with heterogeneity of phenotypic characters of the patients. Once the disease has been diagnosed, every possible effort should be put for all-round evaluation in the disease severity that an individual patient has been affected. Derivation of an effective management plan

Table 2. Characteristics of 23 COPD patients

Attribute	Value
Male (%)	83
Mean age (years)	73±8
Body mass index (kg/m^2)	20.9±5.4
Smoker (%)	87
GOLD stage III and IV (%)	30
MMRC dyspnea scale (1-5)	1.8±1.4
FEV_1 %predicted	67.8±25.4
%FEV_1/FVC	52.0±14.7
IC %predicted	71.3±18.7
TLC %predicted	93.7±18.5
%IC/TLC	31.7±11.1
DLCO %predicted	56.0±28.1
6MWD (m)	321±121
BODE index (0-10)	3.5±2.5
TLVi (L)	4.0±1.12
TLVe (L)	3.0±1.2
NLvi (L)	3.10±0.86
NLVe (L)	2.42±0.92
ELVi (L)	0.9±0.5
ELVe (L)	0.57±0.44
%ELVi	22.2±9.0
%ELVe	17.4±10.0

COPD = chronic obstructive pulmonary disease; GOLD = global initiative for chronic obstructive lung disease; mMRC = modified Medical Research Council; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity; TLC = total lung capacity; DLCO = diffusing capacity; 6MWD = 6-minute walk distance; BODE = body mass index, airflow obstruction, dyspnea, and exercise performance; TLVi = inspiratory total lung volume; TLVe = expiratory total lung volume; NLVi = inspiratory normal lung volume; NLVe = expiratory normal lung volume; ELVi = inspiratory emphysematous lung volume; ELVe = expiratory emphysematous lung volume

Table 3. Correlation analysis for % inspiratory emphysematous lung volume (%ELVi)

Attribute	r	*p*-value
FEV_1 %predicted	-0.33	0.125
%FEV_1/FVC	-0.50	0.016
IC %predicted	-0.37	0.125
TLC %predicted	0.43	0.073
%IC/TLC	-0.51	0.051
DLCO %predicted	-0.58	0.011
MMRC dyspnea scale	0.39	0.070
6MWD	-0.34	0.116
BODE index	0.49	0.017

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity; TLC = total lung capacity; DLCO = diffusing capacity; mMRC = modified Medical Research Council; 6MWD = 6-minute walk distance; BODE = body mass index, airflow obstruction, dyspnea, and exercise performance

Table 4. Correlation analysis for % expiratory emphysematous lung volume (%EVLe)

Attribute	r	*p*-value
FEV_1 %predicted	-0.26	0.235
%FEV_1/FVC	-0.58	0.004
IC %predicted	-0.29	0.243
TLC %predicted	0.46	0.057
%IC/TLC	-0.62	0.014
DLCO %predicted	-0.48	0.042
MMRC dyspnea scale	0.53	0.010
6MWD	-0.50	0.016
BODE index	0.67	<0.001

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity; TLC = total lung capacity; DLCO = diffusing capacity; mMRC = modified Medical Research Council; 6MWD = 6-minute walk distance; BODE = body mass index, airflow obstruction, dyspnea, and exercise performance with minimal side effects from treatment is a particular challenge for general physicians or specialists who take care of the patients. Clinical assessment and physiological defect appraisal have been conventionally used for this specific task. In the era of radiological technique advancement, how can it be incorporated into a personalized COPD care, has become an interesting issue among clinicians.

In the present study, the more advancement of emphysematous lung volumes (high %ELVi and %ELVe), the worse was the diffusion defect (low DLCO %predicted) noted. This may reflect the lung parenchyma destruction that is a key pathology of emphysematous component of COPD. Akira et al had also observed this phenomenon, although their study demonstrated an obvious correlation in the expiratory phase for the patients with more severe airflow limitation[13]. The discrepancy may result from different protocol for radiometric data gathering. Contribution of parenchymal destruction by emphysema to airway limitation, may further explain a negative correlation of %ELVi and %ELVe with the %FEV_1/FVC. In addition, lower %IC/TLC that reflects more air trapping, was well correlated well with emphysema severity during expiration.

In terms of clinical data, only the emphysema severity during expiration could determine subjective assessment (MMRC) and objective test (6MWD) for exercise capacity. This may suggest the dynamic process of airflow limitation, which becomes obvious during increased minute ventilation from exercise. However, the uncertainty about whether there are causal relationships between exercise capacity and anatomical changes from CT scan in patients with COPD should be further elucidated.

When clinical data (body mass index) are combined with physiological data (airflow obstruction and exercise performance), the close correlation between emphysematous lung volumes and BODE index may support the concept of intense local inflammation which disturb systemic dysfunction response in patients with COPD[14]. However, from the study of Chen et al correlation with BODE index was not observed[12]. Different algorithms for measurement, discrepancy of assessment in intervals, and processes other than inflammation may have a potential role.

Theoretically, significant correlation with the percentage of shrink volume, which reflects more air trapping from advanced emphysema, should also be observed with the radiologic quantification. Variation of performing repeated fully inspiration and expiration among each studied patient, may contribute to the negative results in this present study. Although inspiratory scans may have greater accuracy than expiratory scans in detecting emphysema[15], emphysema volume measurement from expiratory CT scans may better reflect pulmonary function test abnormalities in patients with severe emphysema than those from the inspiratory ones[16].

Emphysema quanitification may be a useful tool for early detection of subclinical parenchymal changes in those at risk[17], and for monitoring successful intervention with smoking cessation program in some patients[18]. An application for predicting postoperative pulmonary complication after surgical lung resection has been mentioned recently[19]. Integration of airway measurements may potentiate the predicting power of conventional quantitative CT based on density and volume measurements[20]. Determination of small airways function along with emphysema extent has been shown clearly to characterize physiologic phenotype of patients with COPD[21].

Potential limitation of the present study should be mentioned. First, because of its retrospective nature, confounding factors such as medications and co-morbidities were not controlled. Second, longer intervals between CT study and the pulmonary function with exercise capacity tests could affect the relationship assessment. Lastly, although emphysema quantification has shown its reliability and validity[22], no established standard scoring exists[23-25].

Conclusion

As part of designing a personalized management plan for patients with COPD, severity of emphysema assessed by HRCT can be used as one of various aspects in phenotypic characterization for this multidimensional disease.

What is already known on this topic?

The characteristic of a patient with COPD based on clinical and physiological data, has been used widely for designing a management plan.

What this study adds?

Radiologic emphysema quantification could add essential information for optimum COPD care.

Potential conflicts of interest

None.

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ความสัมพันธ์ระหว่างปริมาณถุงลมโป่งพองกับความรุนแรงของโรคปอดอุดกั้นเรื้อรัง

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วัตถุประสงค์: *เพื่อประเมินความสัมพันธ์ระหว่างปริมาณถุงลมโป่งพองจากการตรวจด้วยเอกซเรย์คอมพิวเตอร์รายละเอียดสูงกับความเปลี่ยนแปลงทางสรีรวิทยาในผู้ป่วยโรคปอดอุดกั้นเรื้อรัง*

วัสดุและวิธีการ: *ได้ทำการศึกษาแบบตัดขวางเพื่อประเมินความรุนแรงของถุงลมโป่งพองในผู้ป่วยโรคปอดอุดกั้นเรื้อรังจำนวน 23 ราย โดยใช้ซอฟต์แวร์สำเร็จรูปจากการตรวจด้วยเอกซเรย์คอมพิวเตอร์รายละเอียดสูงทำการหาความสัมพันธ์กับลักษณะที่แสดงออกของผู้ป่วย ในแง่ความสามารถในการออกกำลัง [modified Medical Research Council (mMRC) dyspnea scale และ 6-minute walk distance (6MWD)] ผลการตรวจสมรรถภาพปอด [สไปโรเมตรีย์ (forced expiratory volume in 1 second, FEV_1 and forced vital capacity, FVC) และ diffusing capacity (DLCO)]*

ผลการศึกษา: *ผู้ป่วยเป็นชาย 19 ราย หญิง 4 ราย อายุเฉลี่ย 73±8 ปี โดยมีค่า FEV_1 %predicted เฉลี่ย 67.8±25.4 ร้อยละของปริมาตรถุงลมโป่งพองขณะหายใจเข้า มีความสัมพันธ์เชิงผกผันอย่างมีนัยสำคัญกับ %FEV_1/FVC, DLCO, ($r = -0.50$, $p = 0.016$) และ DLCO ($r = 0.58$, $p = 0.011$) เช่นเดียวกับร้อยละของปริมาตรถุงลมโป่งพองขณะหายใจออก ($r = -0.58$, $p = 0.004$ สำหรับ %FEV_1/FVC และ $r = 0.48$, $p = 0.042$ สำหรับ DLCO) นอกจากนี้ปริมาตรถุงลมโป่งพองขณะหายใจออกยังมีความสัมพันธ์เชิงผกผันอย่างมีนัยสำคัญกับ 6MWD ($r = 0.50$, $p = 0.016$) แต่ไม่มีความสัมพันธ์อย่างมีนัยสำคัญกับ mMRC scale ($r = 0.53$, $p = 0.01$)*

สรุป: *ความรุนแรงของถุงลมโป่งพองจากการประเมินด้วยเอกซเรย์คอมพิวเตอร์รายละเอียดสูง มีความสัมพันธ์เป็นอย่างดีกับผลการตรวจสมรรถภาพปอด และความสามารถในการออกกำลัง ดังนั้นจึงอาจใช้เป็นองค์ประกอบหนึ่งในการประเมินลักษณะที่แสดงออกของผู้ป่วยโรคปอดอุดกั้นเรื้อรัง เพื่อวางแผนการดูแลรักษาที่มีลักษณะเฉพาะรายบุคคล*
