Original Article | Thoracic Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2021.0033
Korean J Radiol 2021;22(10):1719-1729

Korean Journal of Radiology
KJR

New Method for Combined Quantitative Assessment of Air-Trapping and Emphysema on Chest Computed Tomography in Chronic Obstructive Pulmonary Disease: Comparison with Parametric Response Mapping

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Objective: Emphysema and small-airway disease are the two major components of chronic obstructive pulmonary disease (COPD). We propose a novel method of quantitative computed tomography (CT) emphysema air-trapping composite (EAtC) mapping to assess each COPD component. We analyzed the potential use of this method for assessing lung function in patients with COPD.

Materials and Methods: A total of 584 patients with COPD underwent inspiration and expiration CTs. Using pairwise analysis of inspiration and expiration CTs with non-rigid registration, EAtC mapping classified lung parenchyma into three areas: Normal, functional air trapping (fAT), and emphysema (Emph). We defined fAT as the area with a density change of less than 60 Hounsfield units (HU) between inspiration and expiration CTs among areas with a density less than -856 HU on inspiration CT. The volume fraction of each area was compared with clinical parameters and pulmonary function tests (PFTs). The results were compared with those of parametric response mapping (PRM) analysis.

Results: The relative volumes of the EAtC classes differed according to the Global Initiative for Chronic Obstructive Lung Disease stages ($p < 0.001$). Each class showed moderate correlations with forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) (r = -0.659–0.674, $p < 0.001$). Both fAT and Emph were significant predictors of FEV_1 and FEV_1/FVC (R^2 = 0.352 and 0.488, respectively; $p < 0.001$). fAT was a significant predictor of mean forced expiratory flow between 25% and 75% and residual volume/total vital capacity (R^2 = 0.264 and 0.233, respectively; $p < 0.001$), while Emph and age were significant predictors of carbon monoxide diffusing capacity (R^2 = 0.303; $p < 0.001$). fAT showed better correlations with PFTs than with small-airway disease on PRM.

Conclusion: The proposed quantitative CT EAtC mapping provides comprehensive lung functional information on each disease component of COPD, which may serve as an imaging biomarker of lung function.

Keywords: *Chronic obstructive pulmonary disease; Emphysema; Small-airway disease; Air trapping; Quantitative imaging; Computed tomography*

INTRODUCTION

Emphysema and small-airway disease are the two major components of chronic obstructive pulmonary disease (COPD) [1-3]. Varying combinations and severities of emphysema and small-airway disease can manifest

Received: January 13, 2021 **Revised:** March 23, 2021 **Accepted:** March 26, 2021
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differently among individual patients with COPD, leading to varying degrees of lung function impairment.

Many studies have focused on quantifying these two components using computed tomography (CT). Quantification of emphysema on CT by determining the relative area of the lungs below -950 Hounsfield units (HU) on inspiration CT is an established method that shows significant correlations with airflow obstruction parameters on pulmonary function tests (PFTs) [4-10]. Small-airway disease is quantified indirectly by determining the air-trapping area on CT because of the limited resolution of CT in visualizing small airways. Air trapping is an indicator of small-airway obstruction [11,12]. Several methods for evaluating air trapping, such as quantifying the area below -856 HU on expiration CT (Exp_{-856}), have been reported [7,10,13-15]. The air trapping index (ATI) is a novel method for quantifying air trapping by comparing the densities between inspiration and expiration CT scans using the co-registration method [16]. The ATI defines air trapping as an area with a density increase of less than 60 HU between inspiration and expiration CT scans [17], considering that air trapping is defined as no or less density increase during respiration compared to normal lungs [18]. However, the optimal method for evaluating small-airway disease on CT is still under debate.

Parametric response mapping (PRM) has been introduced to assess each COPD component by performing inspiration and expiration CTs [19]. It allows for differentiation between emphysematous and non-emphysematous air trapping. In PRM, small-airway disease is defined simply as lung areas with densities greater than or equal to -950 HU on inspiration CT and less than -856 HU on expiration CT. However, this method considers only slight dynamic density changes in each voxel and excludes the contribution of emphysema to air trapping in assessing small-airway disease.

Hence, in this study, we proposed a novel method of CT analysis of two major disease components of COPD: emphysema air-trapping composite (EAtC) mapping, using quantitative CT analysis of emphysema and ATI in the co-registration of inspiration and expiration CT scans. We analyzed the potential use of this method as an imaging biomarker for assessing lung function in patients with COPD and compared this method with PRM.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Institutional Review Board of our medical center (IRB No. 2012-0226 and 2013-1032), and written informed consent was obtained from all patients. All patients were selected from the Korean Obstructive Lung Disease (KOLD) [20] and KOLD 2 Cohorts (Supplementary Materials 1). From these two cohorts, 584 patients with COPD who were available for baseline inspiration and expiration CT and PFT results were included in this study between June 2005 and June 2015 (Fig. 1). All patients underwent volumetric inspiration and expiration CT scans, as well as PFTs with spirometry, lung volumes, and diffusion capacity measurements. PFTs were performed on the same day or within 2 weeks of CT scans, according to the guidelines [21-23]. The St. George's Respiratory Questionnaire (SGRQ) questionnaire was used to assess the degree of dyspnea [24]. Other clinical variables were also assessed, such as the exercise capacity of a six-minute walk distance, the degree of dyspnea according to the modified Medical Research Council dyspnea scale, and body mass index. The Body mass index, airflow Obstruction, Dyspnea and Exercise capacity (BODE) index was calculated [25]. Of the 584 patients, 174 were included in the study population of a previous report [17]. A previous study assessed the optimal ATI threshold for quantifying air trapping; in this study, we used the modified ATI method.

CT Examination

Volumetric CT scans were obtained in the supine position at both full inspiration and expiration using one of the following scanners: Somatom Sensation 16, Definition AS+ or Definition Flash (Siemens Healthineers) (n = 463) at 140

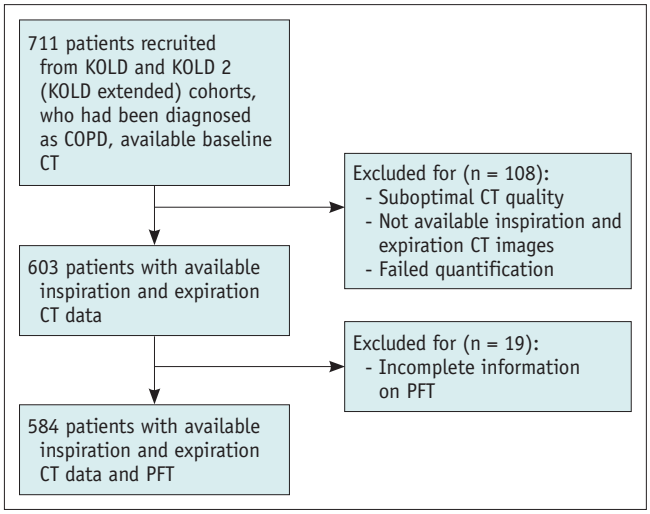

Fig. 1. Flow diagram of patient inclusion. KOLD = Korean Obstructive Lung Disease, PFT = pulmonary function test

https://doi.org/10.3348/kjr.2021.0033

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kVp and 100 effective mAs or Brilliance 40 or 64 (Philips Medical Systems) (n = 121) at 140 kVp and 100–135 effective mAs with a pitch of 1.0, and collimation of 0.75 or 0.625 mm. The CT data were reconstructed at a 0.75-mm slice thickness and 0.7-mm increment using a B30f kernel (Siemens Healthineers) or at a 0.8-mm slice thickness and 0.8-mm increment or a 0.67-mm slice thickness and 0.67-mm increment using a standard reconstruction algorithm (B or C kernel) (Philips Medical System). All CT scanners were calibrated weekly using an American Association of Physicists in Medicine standard phantom.

Quantitative CT EAtC Mapping

Quantitative CT EAtC mapping was performed using an automatic segmentation software (Aview, Coreline Soft). Lung segmentation was performed for EAtC mapping, and the airways, vessels, and background were segmented and removed from the lung parenchyma using several specific thresholds [16]. Inspiration and expiration CT images were registered using a non-rigid method. A detailed description of the registration of inspiration and expiration CT images has been documented in a previous study [16].

In EAtC mapping, the lung parenchyma is classified into three lung areas: 1) areas with functional air trapping (fAT), 2) areas with emphysema (Emph), and 3) areas with normal lung parenchyma (Normal) (Fig. 2). Emph was defined as the volume fraction of voxels exhibiting a density lower than -950 HU on inspiration CT; fAT was defined as the volume fraction of voxels exhibiting a change in density of less than 60 HU between inspiration and co-registered expiration CT scans [17] in the lung parenchyma sufficiently inflated on inspiration CT with a lung density less than -856 HU. The remaining volume fraction was defined as Normal. The value of -856 HU was chosen because it is the mean attenuation of a normally inflated lung on inspiration (Supplementary Materials 2, Supplementary Table 1) [26]. Each lung area was presented as its volume relative to the total lung volume.

Parametric Response Mapping

We also performed a PRM analysis of the CT scans of our study population [19]. After segmentation of the lungs and registration of inspiration and expiration CT images, the lung parenchyma was classified into three lung areas as documented in a previous study [19]: functional small-airway disease (PRM_{fSAD}), emphysema (PRM_{Emph}), and normal lung (PRM_{Normal}).

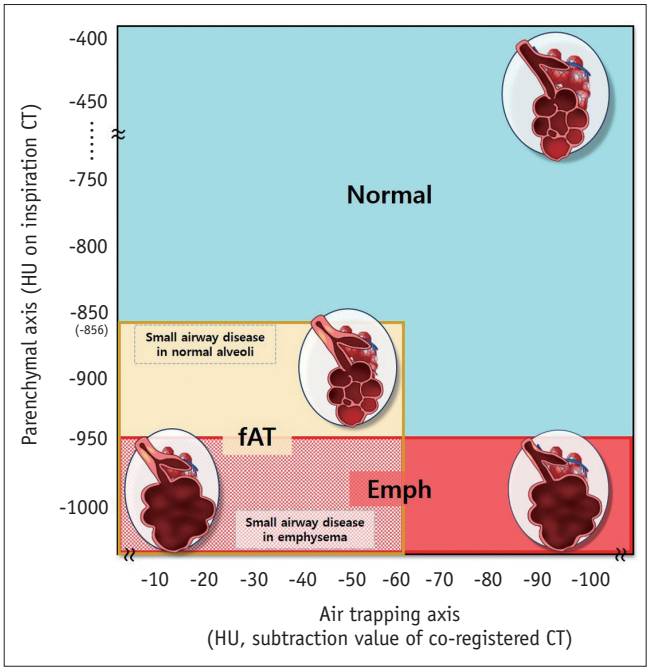

Fig. 2. The concept of quantitative CT EAtC mapping.
Quantitative CT EAtC mapping classifies whole lung parenchyma into three areas: Normal, fAT, and Emph, using the pairwise analysis of inspiration and expiration CT scans with non-rigid registration. fAT may include areas with small-airway disease in normal alveoli and in emphysematous destruction. Emph includes all areas with emphysematous destruction in the lung. The rest of the lung areas are classified as Normal. EAtC = emphysema air-trapping composite, Emph = emphysema, fAT = functional air trapping, HU = Hounsfield units, Normal = normal lung parenchyma by EAtC

Statistical Analysis

Each class of EAtC mapping was compared according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [27] using a one-way analysis of variance test. The relationships of each EAtC class with PFTs and clinical findings, including the BODE index and SGRQ score, were assessed using Pearson's correlation or Spearman's correlation. Multiple linear regression analysis with stepwise selection was performed to determine the predictors of PFT parameters and BODE index. EAtC classes and clinical variables, such as age and smoking history (pack-years), were used as independent variables. The relative volumes of each EAtC and PRM classes were compared using paired *t* tests. The relationships of each PRM class with the PFTs, BODE index, and SGRQ score were also assessed. Correlation coefficients were interpreted according to the following categories: $r < 0.3$, weak correlation; $0.3 < r < 0.7$, moderate correlation; and $r > 0.7$, strong correlation. Correlation statistics of EAtC mapping and PRM analysis were compared using the

https://doi.org/10.3348/kjr.2021.0033

Hittner's test [28]. Statistical significance was set at $p < 0.05$. All statistical analyses, except for Hittner's test, were performed using SPSS Statistics for Windows, version 21 (IBM Corp.). Hittner's test was performed using R software version 3.6.1 (R Project for Statistical Computing).

Table 1. Patients Characteristics

Variables	Data
Age, year	65.7 ± 11.7
Sex, male:female	542:42
Pack-years	44.5 ± 26.7
GOLD stage	
I	85
II	333
III	144
IV	22
BODE index	2.70 ± 1.95
Pulmonary function tests	
FEV_1, liter	1.6 ± 0.6
FEV_1, % predicted	52.2 ± 16.5
FVC, liter	3.3 ± 0.9
FVC, % predicted	79.8 ± 16.4
FEV_1/FVC, %	46.7 ± 11.1
$FEF_{25-75\%}$, % predicted	20.9 ± 10.7
DL_{CO}, % predicted	75.7 ± 22.9
RV, % predicted	114.6 ± 57.8
TLC, % predicted	103.6 ± 22.9
RV/TLC, %	41.3 ± 14.2
6MWD, meter	417.9 ± 88.4
SGRQ score	30.5 ± 18.6

Data are presented as mean ± standard deviation except sex and GOLD stages of which the data are number of patients. BODE = Body mass index, airflow Obstruction, Dyspnea and Exercise capacity, DL_{CO} = carbon monoxide diffusing capacity corrected for hemoglobin concentration, $FEF_{25-75\%}$ = mean forced expiratory flow between 25% and 75% of FVC, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Obstructive Lung Disease, RV = residual volume, SGRQ = St. George's Respiratory Questionnaire, TLC = total lung capacity, 6MWD = six-minute walk distance

RESULTS

Patient characteristics are summarized in Table 1. The relative volumes of the EAtC classes showed significant differences according to GOLD stage ($p < 0.001$) (Table 2, Figs. 3, 4). With an increase in GOLD stage, fAT and Emph increased, while Normal significantly decreased. Post-hoc analysis showed significant intergroup differences in EAtC classes between GOLD stages ($p < 0.05$), except between Emph of GOLD I and GOLD II.

Association of EAtC Classes with PFTs and Other Clinical Parameters

The associations of each EAtC class with the PFTs, BODE

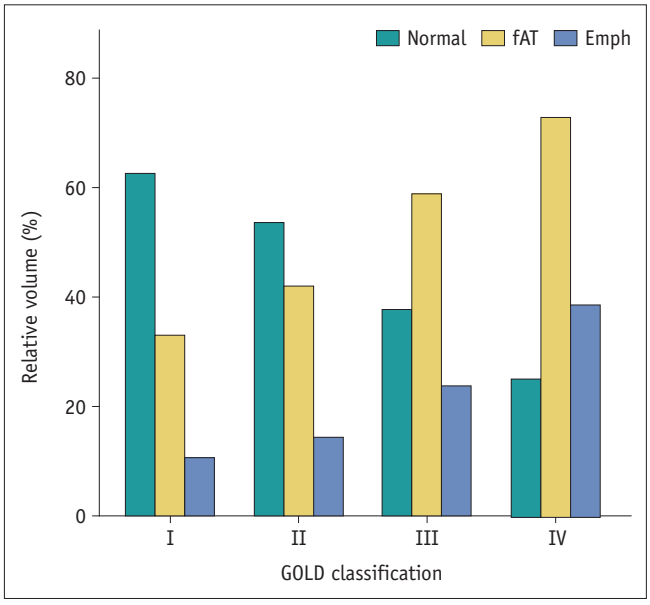

Fig. 3. Distribution of EAtC classes according to GOLD stages. The relative volumes of EAtC classes showed distinctly different distributions according to GOLD severity; fAT and Emph increased, whereas Normal decreased, with an increase in GOLD stage. EAtC = emphysema air-trapping composite, Emph = emphysema by EAtC, fAT = functional air trapping by EAtC, GOLD = Global Initiative for Obstructive Lung Disease, Normal = normal lung parenchyma by EAtC

Table 2. Characteristics of CT-Quantitative EAtC Mapping of Lung Parenchyma According to GOLD Stages

EAtC Mapping	GOLD Stage				*P**
	I (n = 85)	II (n = 333)	III (n = 144)	IV (n = 22)	
Normal	62.4 ± 19.8	53.5 ± 17.6	37.7 ± 14.5	24.8 ± 7.3	< 0.001
fAT	32.9 ± 20.0	42.0 ± 18.1	58.8 ± 15.0	72.8 ± 7.8	< 0.001
Emph	10.5 ± 11.6	14.2 ± 11.3	23.7 ± 15.0	38.6 ± 12.2	< 0.001

Data are presented as means ± standard deviations of the relative volume (%) of each class. *EAtC classes were compared according to GOLD stages using one-way analysis of variance. Post-hoc analysis with Tukey's test showed the significant inter-group differences between all GOLD stages ($p < 0.05$) except among Emph in GOLD stages I and II. EAtC = emphysema air-trapping composite, Emph = emphysema by EAtC, fAT = functional air trapping by EAtC, GOLD = Global Initiative for Obstructive Lung Disease, Normal = normal lung parenchyma by EAtC

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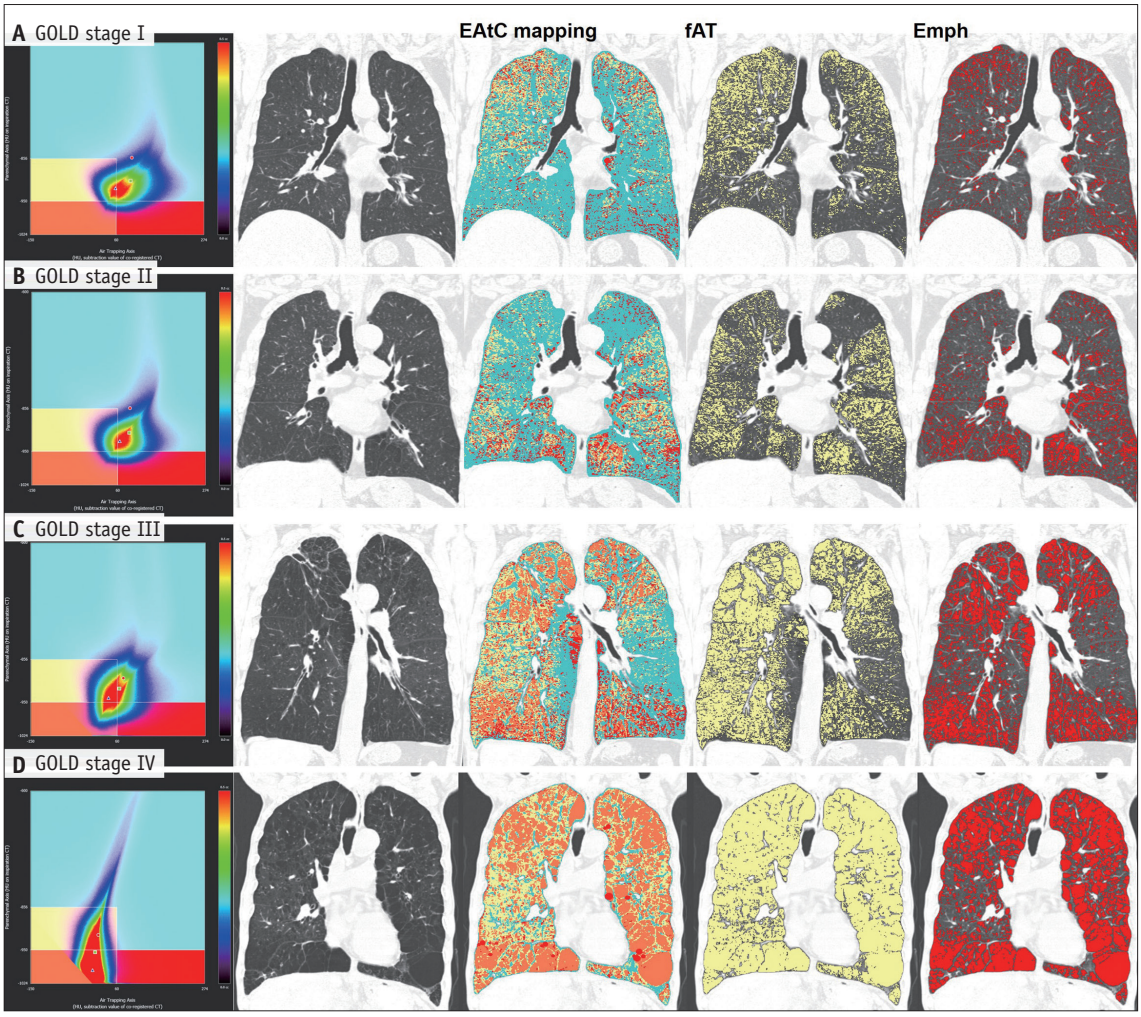

Fig. 4. Images of EAtC mapping of patients with chronic obstructive pulmonary disease in each GOLD stage. The first column shows the distribution of voxels corresponding to each EAtC class. Color-mapped CT images show the distribution of each EAtC class within the lung parenchyma. In the EAtC mapping images, areas with fAT are displayed in yellow, areas with Emph are displayed in red, and areas with Normal are displayed in blue. The area marked in orange is where fAT and Emph overlap. According to the GOLD severity, the distribution of voxels in each EAtC class appeared differently.
A. Coronal image obtained from inspiration CT of a GOLD stage I patient showed minimal centrilobular emphysema in both upper lobes. In this patient, fAT and Emph were 22% and 11%, respectively. **B.** Coronal image obtained from inspiration CT of a GOLD stage II patient showed mild centrilobular emphysema in both lungs. In this patient, fAT and Emph were 24% and 15%, respectively. **C.** Coronal image obtained from inspiration CT in a GOLD stage III patient showed mild to moderate centrilobular and paraseptal emphysema in both lungs. In this patient, fAT and Emph were 41% and 27%, respectively. **D.** Coronal image obtained from inspiration CT in a GOLD stage IV patient showed confluent and advanced destructive emphysema in both lungs. In this patient, fAT and Emph were 76% and 54%, respectively. EAtC = emphysema air-trapping composite, Emph = emphysema by EAtC, fAT = functional air trapping by EAtC, GOLD = Global Initiative for Obstructive Lung Disease, Normal = normal lung parenchyma by EAtC

index, and SGRQ score are presented in Table 3. fAT and Emph showed significant and moderate negative correlations with forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) (fAT: r = -0.567 and -0.659, Emph: r = -0.430 and -0.605, respectively, all $p < 0.001$), which are measures of airflow limitation. fAT showed the highest correlation with mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$), residual volume (RV), and RV/total lung capacity (TLC) (r = -0.502–0.491, $p <$ 0.001), which are measures of pulmonary air trapping or small-airway dysfunction, while Emph showed the highest correlation with the carbon monoxide diffusing capacity corrected for hemoglobin concentration (DL_{CO}) (r = -0.516, $p < 0.001$), which is a measure of parenchymal destruction. Each class also showed moderate correlations with the BODE index and SGRQ score, which are integrative prognostic factors of COPD and measures of health impairment, respectively. Table 4 shows results of the multiple linear

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Table 3. Correlation of CT-Quantitative EAtC Mapping and PRM Classes with PFTs, BODE Index, and SGRQ Score

Method	PFTs and Clinical Variables								
	FEV_1	FEV_1/FVC	$FEF_{25-75\%}$	RV	TLC	RV/TLC	DL_{CO}	BODE Index	SGRQ
EAtC									
Normal	0.559	0.674	0.500	-0.475	-0.471	-0.452	0.361	-0.561	-0.349
fAT	-0.567	-0.659	-0.502	0.491	0.469	0.474	-0.333	0.584	0.354
Emph	-0.430	-0.605	-0.423	0.327	0.384	0.280	-0.516	0.425	0.256
PRM									
PRM_{Normal}	0.547	0.661	0.463	-0.454	-0.454	-0.426	0.349	-0.533	-0.324
PRM_{fSAD}	-0.383	-0.411	-0.337	0.331	0.279	0.345	-0.041*	0.319	0.191
PRM_{Emph}	-0.488	-0.647	-0.471	0.366	0.407	0.326	-0.502	0.475	0.275

Data are presented as correlation coefficients determined using the Pearson's correlation test for Normal, fAT, PRM_{Norm} and PRM_{fSAD} and Spearman's correlation for Emph and PRM_{Emph}. *p values > 0.05. Otherwise, p values < 0.05. BODE = Body mass index, airflow Obstruction, Dyspnea and Exercise capacity, DL_{CO} = carbon monoxide diffusing capacity corrected for hemoglobin concentration, EAtC = emphysema air-trapping composite, Emph = emphysema by EAtC, fAT = functional air trapping by EAtC, $FEF_{25-75\%}$ = mean forced expiratory flow between 25% and 75% of FVC, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, Normal = normal lung parenchyma by EAtC, PFT = pulmonary function test, PRM = parametric response mapping, PRM_{Emph} = emphysema by PRM, PRM_{fSAD} = functional small airways disease by PRM, PRM_{Normal} = normal lung by PRM, RV = residual volume, SGRQ = St. George's Respiratory Questionnaire, TLC = total lung capacity

Table 4. Multiple Linear Regression Analysis for CT-Quantitative EAtC Mapping and Clinical Variables (Age, Pack-Years) for PFTs and BODE Index

Variables	Coefficients	*P*	R^2
FEV_1			0.352
fAT	-0.409	< 0.001	
Emph	-0.188	< 0.001	
FEV_1/FVC			0.488
fAT	-0.277	< 0.001	
Emph	-0.224	< 0.001	
$FEF_{25-75\%}$			0.264
fAT	-0.281	< 0.001	
RV/TLC			0.233
fAT	0.344	< 0.001	
DL_{CO}			0.303
Emph	-0.891	< 0.001	
Age	-0.153	0.038	
BODE index			0.397
fAT	0.425	< 0.001	
Emph	0.253	< 0.001	
Age	0.087	0.022	

The following independent variables were used for the multivariable model: EAtC classes (fAT and Emph), age, and smoking history (pack-years). Normal from the EAtC classes was not considered as an independent variable because considerable multicollinearity (variance inflation factor > 10) between fAT and Normal were found. BODE = Body mass index, airflow Obstruction, Dyspnea and Exercise capacity, DL_{CO} = carbon monoxide diffusing capacity corrected for hemoglobin concentration, EAtC = emphysema air-trapping composite, Emph = emphysema by EAtC, fAT = functional air trapping by EAtC, $FEF_{25-75\%}$ = mean forced expiratory flow between 25% and 75% of FVC, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, Normal = normal lung parenchyma by EAtC, PFT = pulmonary function test, RV = residual volume, TLC = total lung capacity

regression analysis of EAtC classes and clinical parameters for predicting the PFTs and BODE index results. Among the EAtC classes, considerable multicollinearity (variance inflation factor > 10) between fAT and Normal were found. Hence, fAT and Emph were included as independent variables. Both fAT and Emph were identified as predictors of FEV_1 and FEV_1/FVC (R^2 = 0.352 and 0.488, respectively; p < 0.001). For $FEF_{25-75\%}$ and RV/TLC, fAT was the only significant predictor (R^2 = 0.264 and 0.233, both p < 0.001), while Emph and patient age were significant predictors of DL_{CO} (R^2 = 0.303, p < 0.001).

Comparison of EAtC Mapping and PRM Analysis

The results of the EAtC mapping and PRM analysis are summarized in Supplementary Table 2. The mean relative volumes of Normal vs. PRM_{Normal}, fAT vs. PRM_{fSAD}, and Emph vs. PRM_{Emph} were compared, and they differed significantly between the two methods (p < 0.05). The mean relative volume of fAT was significantly higher than that of PRM_{fSAD}, and that of Emph was higher than that of PRM_{Emph}. Each PRM class also showed a significant correlation with the PFT results, BODE index, and SGRQ score (Table 3). When the correlation statistics were compared between EAtC mapping and PRM, fAT showed significantly stronger correlations with PFT results, including $FEF_{25-75\%}$, RV, and RV/TLC than PRM_{fSAD} (all, p < 0.001) (Fig. 5). PRM_{Emph} showed slightly stronger correlations with most of the PFT results than Emph of EAtC mapping (p < 0.001); however, Emph showed a slightly stronger correlation with DL_{CO} than PRM_{Emph}, although this trend was not statistically significant (p =

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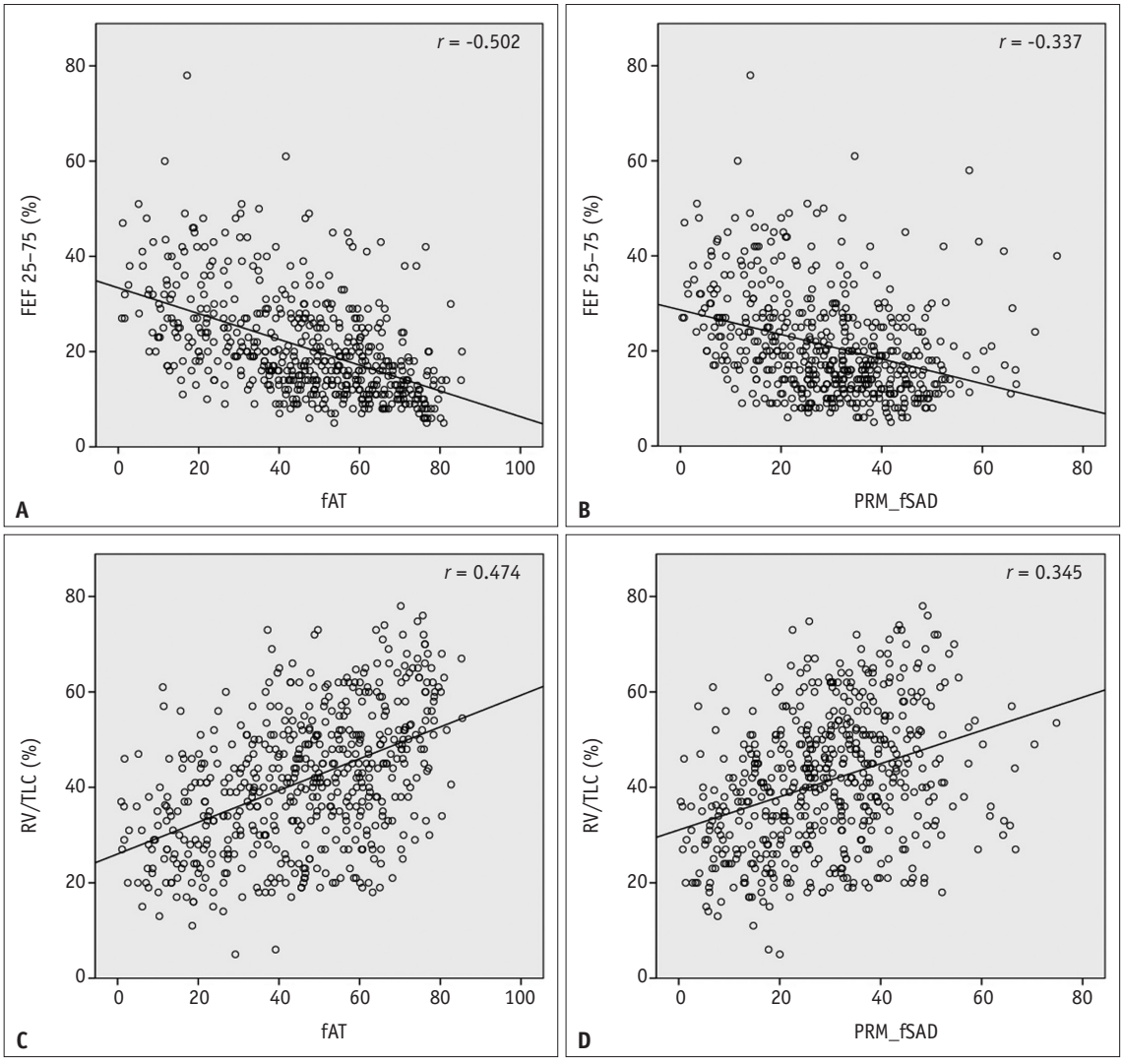

Fig. 5. Comparison between fAT and PRM_{fSAD} in correlation with $FEF_{25–75\%}$ and RV/TLC.
A-D. The correlation coefficients of fAT and PRM_{fSAD} were **(A)**, -0.502 and **(B)**, -0.337 for $FEF_{25–75\%}$ and **(C)**, 0.474 and **(D)**, 0.345 for RV/TLC. There were significant differences in correlation coefficients between fAT and PRM_{fSAD} for both $FEF_{25–75\%}$ and RV/TLC ($p < 0.001$). fAT = functional air trapping by emphysema air-trapping composite, $FEF_{25–75\%}$ = mean forced expiratory flow between 25% and 75% of forced vital capacity, PRM_{fSAD} = functional small-airway disease by PRM, RV = residual volume, TLC = total lung capacity

0.079) (Supplementary Table 3).

DISCUSSION

This study showed that each disease component of COPD quantified using EAtC mapping showed progression with increased disease severity according to the GOLD criteria and each component was significantly associated with PFTs and clinical variables. EAtC classes were significant imaging predictors of PFT parameters and the BODE index. When the correlation with lung function was compared between EAtC mapping and PRM, fAT showed significantly stronger correlations with PFT results, including $FEF_{25–75\%}$, RV, and RV/TLC, than PRM_{fSAD}. In this respect, EAtC mapping can provide a comprehensive view of each COPD component contributing to the current lung function impairment using the modified ATI. In this study, we focused on the association between EAtC classes and lung function in patients with COPD; thus, the potential use of this method for disease follow-up or assessment of treatment responses should be studied in the future.

PRM analysis may have a unique potential for early identification of disease progression in COPD [29,30] by identifying non-emphysematous air trapping, or early small-airway disease. The focus of EAtC mapping is different from that of PRM analysis. EAtC mapping aims

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to evaluate the factors contributing to lung function impairments in individual patients by evaluating the extent and distribution of each COPD component more accurately and comprehensively. It is important to detect the preclinical disease of COPD, which can be a potential target for treatment. However, considering that patients with COPD manifest various lung function declines and treatment plans are devised based on lung function evaluations, accurately evaluating each disease component contributing to various lung function impairments on CT may be helpful in understanding a patient's current status and planning treatment. EAtC mapping may also be used to evaluate how each disease component that affects lung function impairments changes with the progression of COPD. Moreover, air trapping in the non-emphysematous area within fAT can be assessed separately using the EAtC mapping segmentation software, although this area was not evaluated in this study. In previous studies, air trapping in non-emphysematous and emphysematous areas have been separately evaluated using ATI analysis [16,17]. The air trapping in the non-emphysematous area within fAT may correspond with PRM_{fSAD} or more accurately reflect early small-airway disease using the ATI method.

fAT includes air trapping in the emphysematous area (small-airway disease with emphysematous destruction) and non-emphysematous areas (small-airway disease with normal alveoli). Indeed, air trapping in the emphysematous area might be controversial in assessing small-airway disease. Although small-airway disease precedes emphysematous destruction [31,32], preexisting small-airway disease may co-exist in areas with emphysema, and further narrowing caused by emphysematous destruction of the supporting structures of small airways may also worsen air trapping. Therefore, small-airway disease in both normal alveoli and emphysematous areas may affect air trapping. A previous study revealed that air trapping in emphysematous areas may substantially contribute to small-airway dysfunction [17]. Our study also demonstrated similar results and showed that fAT showed significantly better correlations with PFTs than PRM_{fSAD}, which represents non-emphysematous air trapping only. With respect to functional assessments on chest CT, fAT may characterize small-airway dysfunction better than PRM_{fSAD}.

The optimal method for quantifying air trapping on CT is still under debate. The ATI analyzes density changes between co-registered inspiration and expiration CT scans [16,17], whereas the other CT indices of air trapping such as PRM_{fSAD}, Exp_{-856}, or expiration/inspiration ratio of the mean lung density use the fixed HU values on expiration or inspiration CT scans. Considering that air trapping is defined as an area that shows no or less density increase during expiration than normal lungs on CT [18], the ATI is a logical method that considers dynamic changes. The ATI was significantly correlated with PFTs and was comparable to the other CT indices of air trapping in previous studies [16,17]. In EAtC mapping, air trapping was quantified using the modified ATI and presented as fAT, which was significantly correlated with PFTs.

In EAtC mapping, the ATI was modified by excluding the lung areas with densities higher than -856 HU on the inspiration CT from the air trapping area. This value is the attenuation of a normally inflated lung on inspiration CT [26], and it is presumed that the lung areas showing density changes less than 60 HU but a density higher than -856 HU on inspiration CT, inflated incompletely or insufficiently, result in small density changes on expiration CT. Therefore, we speculated that these lung areas may be associated with normal lung parenchyma, such as structural components that are not actively involved in gas exchange, and not with air-trapping areas. The modified ATI (fAT) showed stronger correlations with PFTs than the original ATI (of the whole lung area).

The extent of emphysema assessed on chest CT provides information on the degree of lung parenchymal destruction in patients with COPD. In our study, Emph was significantly associated with DL_{CO}, which is in accordance with previous studies [7,33,34]. Increasing emphysema could cause hypoxemia through impaired diffusion capacity and loss of surface area for gas exchange [35]. Therefore, Emph may possibly identify lung areas with destroyed alveoli that can lead to gas exchange impairment. Although Emph and fAT partly overlap in the lung on EAtC mapping, Emph and fAT may provide information on lung parenchymal destruction and small-airway dysfunction, respectively.

Our study has several limitations. First, the retrospective design of the study could have caused selection bias. Second, we modified the ATI using a threshold of -856 HU on inspiration CT. Although it is known that this value reflects the attenuation of a normally inflated lung on inspiration CT, we could not histologically confirm our assumption. Despite this, the modified ATI showed stronger correlations with the PFTs than the original ATI. Third, the optimal threshold for density changes of ATI was determined using a single CT protocol and CT machine in a

https://doi.org/10.3348/kjr.2021.0033

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previous study [17]. The predetermined threshold can vary according to the CT machines, section thicknesses, and reconstruction algorithms. However, all CT scanners were regularly calibrated, and most CT images were obtained from the same CT machine with the same CT protocol as in the previous study. Nonetheless, further external validation under different conditions is necessary. Fourth, although CT protocols of the KOLD cohort were designed to minimize interpatient differences, CT machines vary between centers. The detailed reconstruction algorithms or voltages of the CT scans also varied slightly by the CT manufacturer. This may have affected the CT parameters in our study. Recently, attempts have been made to develop deep learning-based post-processing techniques that permit interconversion among CT images obtained using different CT protocols [36,37]. This method has the potential to facilitate reliable quantification of CT scans obtained using different protocols and machines. Lastly, as CT was obtained without spirometric control, there was a possibility of variations in the expiration level, which may have influenced the air-trapping quantification. However, we instructed the patients sufficiently regarding the appropriate inspiratory and expiratory levels before CT scanning, although rigorous volume control was difficult.

In conclusion, quantitative CT EAtC mapping can provide spatial and quantitative information on the two disease components of COPD, emphysema and small-airway disease, which are associated with COPD severity and lung function status. This method has the potential to serve as an imaging biomarker for assessing lung function in patients with COPD by comprehensively evaluating these components.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2021.0033.

Conflicts of Interest

Joon Beom Seo and Namkug Kim have a patent: method for automatic quantification of air trapping on chest CT data (Patent No. KR-10-0979335). Joon Beom Seo, Sangmin Lee and Namkung Kim are stockholders of Coreline Soft and received royalties for licensing the patent and knowhow of image quantification. Jaeyoun Yi is an employee of Coreline Soft, which is a company that develops software to enable quantitative analysis of medical images. All other authors declare no competing interests. This research did not receive any specific grant from agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors would like to acknowledge Seon Ok Kim, Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, for contributions to statistical analysis in this study.

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REFERENCES

1. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:S77-S121
2. Agustí A, Vestbo J. Current controversies and future perspectives in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011;184:507-513
3. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med* 2010;182:598-604
4. Bergin C, Müller N, Nichols DM, Lillington G, Hogg JC, Mullen B, et al. The diagnosis of emphysema. A computed tomographic-pathologic correlation. *Am Rev Respir Dis* 1986;133:541-546
5. Gevenois PA, De Vuyst P, de Maertelaer V, Zanen J, Jacobovitz D, Cosio MG, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1996;154:187-192
6. Gould GA, Redpath AT, Ryan M, Warren PM, Best JJ, Flenley DC, et al. Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. *Eur Respir J* 1991;4:141-146
7. Lee YK, Oh YM, Lee JH, Kim EK, Lee JH, Kim N, et al. Quantitative assessment of emphysema, air trapping, and airway thickening on computed tomography. *Lung* 2008;186:157-165
8. Müller NL, Staples CA, Miller RR, Abboud RT. "Density mask". An objective method to quantitate emphysema using computed tomography. *Chest* 1988;94:782-787
9. Park YS, Seo JB, Kim N, Chae EJ, Oh YM, Lee SD, et al. Texture-based quantification of pulmonary emphysema on high-resolution computed tomography: comparison with density-based quantification and correlation with pulmonary function test. *Invest Radiol* 2008;43:395-402
10. Schroeder JD, McKenzie AS, Zach JA, Wilson CG, Curran-Everett D, Stinson DS, et al. Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. *AJR Am J Roentgenol* 2013;201:W460-W470
11. Lee KW, Chung SY, Yang I, Lee Y, Ko EY, Park MJ. Correlation of aging and smoking with air trapping at thin-section CT of the lung in asymptomatic subjects. *Radiology* 2000;214:831-836
12. Tanaka N, Matsumoto T, Miura G, Emoto T, Matsunaga N, Ueda K, et al. Air trapping at CT: high prevalence in asymptomatic subjects with normal pulmonary function. *Radiology* 2003;227:776-785
13. Akira M, Toyokawa K, Inoue Y, Arai T. Quantitative CT in chronic obstructive pulmonary disease: inspiratory and expiratory assessment. *AJR Am J Roentgenol* 2009;192:267-272
14. Kubo K, Eda S, Yamamoto H, Fujimoto K, Matsuzawa Y, Maruyama Y, et al. Expiratory and inspiratory chest computed tomography and pulmonary function tests in cigarette smokers. *Eur Respir J* 1999;13:252-256
15. Mets OM, van Hulst RA, Jacobs C, van Ginneken B, de Jong PA. Normal range of emphysema and air trapping on CT in young men. *AJR Am J Roentgenol* 2012;199:336-340
16. Kim EY, Seo JB, Lee HJ, Kim N, Lee E, Lee SM, et al. Detailed analysis of the density change on chest CT of COPD using non-rigid registration of inspiration/expiration CT scans. *Eur Radiol* 2015;25:541-549
17. Lee SM, Seo JB, Lee SM, Kim N, Oh SY, Oh YM. Optimal threshold of subtraction method for quantification of air-trapping on coregistered CT in COPD patients. *Eur Radiol* 2016;26:2184-2192
18. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008;246:697-722
19. Galbán CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med* 2012;18:1711-1715
20. Park TS, Lee JS, Seo JB, Hong Y, Yoo JW, Kang BJ, et al. Study design and outcomes of Korean obstructive lung disease (KOLD) cohort study. *Tuberc Respir Dis (Seoul)* 2014;76:169-174
21. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;26:720-735
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-338
23. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511-522
24. Kim YS, Byun MK, Jung WY, Jeong JH, Choi SB, Kang SM, et al. Validation of the Korean version of the St. George's respiratory questionnaire for patients with hronic respiratory disease. *Tuberc Respir Dis* 2006;61:121-128
25. 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;350:1005-1012
26. Lynch DA. Progress in imaging COPD, 2004-2014. *Chronic Obstr Pulm Dis* 2014;1:73-82
27. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med* 2017;195:557-582
28. Hittner JB, May K, Silver NC. A Monte Carlo evaluation of tests for comparing dependent correlations. *J Gen Psychol* 2003;130:149-168

https://doi.org/10.3348/kjr.2021.0033

29. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, et al. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2016;194:178-184
30. Boes JL, Hoff BA, Bule M, Johnson TD, Rehemtulla A, Chamberlain R, et al. Parametric response mapping monitors temporal changes on lung CT scans in the subpopulations and intermediate outcome measures in COPD Study (SPIROMICS). *Acad Radiol* 2015;22:186-194
31. Hogg JC, McDonough JE, Suzuki M. Small airway obstruction in COPD: new insights based on micro-CT imaging and MRI imaging. *Chest* 2013;143:1436-1443
32. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011;365:1567-1575
33. Mohamed Hoesein FA, de Jong PA, Lammers JW, Mali WP, Mets OM, Schmidt M, et al. Contribution of CT quantified emphysema, air trapping and airway wall thickness on pulmonary function in male smokers with and without COPD. *COPD* 2014;11:503-509
34. Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000;162:1102-1108
35. Saure EW, Bakke PS, Lind Eagan TM, Aanerud M, Jensen RL, Grydeland TB, et al. Diffusion capacity and CT measures of emphysema and airway wall thickness - relation to arterial oxygen tension in COPD patients. *Eur Clin Respir J* 2016;3:29141
36. Lee SM, Lee JG, Lee G, Choe J, Do KH, Kim N, et al. CT image conversion among different reconstruction kernels without a sinogram by using a convolutional neural network. *Korean J Radiol* 2019;20:295-303
37. Bak SH, Kim JH, Jin H, Kwon SO, Kim B, Cha YK, et al. Emphysema quantification using low-dose computed tomography with deep learning-based kernel conversion comparison. *Eur Radiol* 2020;30:6779-6787

 https://doi.org/10.3348/kjr.2021.0033