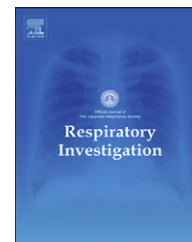




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## Review

## Recent findings in chronic obstructive pulmonary disease by using quantitative computed tomography

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## ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by an incompletely reversible airflow limitation that results from a combination of airway wall remodeling and emphysematous lung destruction. Forced expiratory volume in 1 s (FEV<sub>1</sub>) has been considered the gold standard for diagnosis, classification, and follow-up in patients with COPD, but it has certain limitations and it is still necessary to find other noninvasive modalities to complement FEV<sub>1</sub> to evaluate the effect of therapeutic interventions and the pathogenesis of COPD. Quantitative computed tomography (CT) has partly met this demand. The extent of emphysema and airway dimensions measured using quantitative CT are associated with morphological and functional changes and clinical symptoms in patients with COPD. Phenotyping COPD based on quantitative CT has facilitated interventional and genotypic studies. Recent advances in COPD findings with quantitative CT are discussed in this review.

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Abbreviations:  $\sqrt{Aaw}$  at Pi10, the square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm; Ai, airway internal area; Ao, airway outer area; Awa, airway wall area; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CSA, cross-sectional area of small pulmonary vessels; CT, computed tomography;  $D_{LCO}$ , diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HU, Hounsfield unit; ICS, inhaled corticosteroid; LAA, low attenuation area; LAA%, the percentage of low attenuation area; LVRS, lung volume reduction surgery; RV, residual volume; TLC, total lung capacity; VA, alveolar volume; WA%, the percentage of wall area

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## 1. Introduction

Chronic obstructive pulmonary disease (COPD) was estimated to have caused approximately 2.75 million deaths and 27.76 million disability-adjusted life years worldwide in 2002 [1]. COPD is expected to be the third leading cause of death and the fifth leading cause of morbidity in the world by the year 2020 [2]. The pulmonary component of COPD is characterized by airflow limitation that is not fully reversible [3]. Airflow limitation is defined by pulmonary function test results and is caused by narrowing of small airways [4,5], which is a consequence of a combination of airway wall thickening due to airway wall remodeling and loss of tethering force due to emphysematous lung destruction [6]. To fully evaluate these morphological abnormalities in patients with COPD, lung specimens are needed. However, lung biopsy is not a feasible option for most patients who participate in cross-sectional or longitudinal studies [7]. With advances in computed tomography (CT) technology combined with visual scoring systems or CT image analysis programs, i.e., computer algorithms that can be used to analyze CT data, herein referred to as quantitative CT, these morphological changes can now be analyzed in detail in a relatively non-invasive manner. Quantitative CT in COPD has been used to evaluate severity of emphysema, and to assess airway dimensions and small pulmonary vessels on CT images. These methods allow for comparison of CT abnormalities between patients or observation of progression of disease within a single patient. Recent findings in COPD using quantitative CT are discussed in this review.

## 2. Extent of emphysema

Emphysema is characterized by permanently enlarged airspaces distal to the terminal bronchiole with destruction of the alveolar wall [8,9]. It is generally classified as centrilobular, panlobular, or paraseptal [10,11]. The CT appearance of emphysema features low attenuation areas (LAAs) [12,13]. In order to quantify severity, the percentage of low attenuation areas (LAA%), which implies the extent of emphysema, is calculated. The LAA% of each CT section is the ratio of the LAAs to the total lung area multiplied by 100 [14].

Initially, the extent of emphysema visualized was quantified as an emphysema score. The emphysema score of a section is 0 if its LAA% is <5%, 1 from 5% to <25%, 2 from 25% to <50%, 3 from 50% to <75%, and 4 if  $\geq 75\%$  [15]. However, this method is time-consuming and generates intra-observer and inter-observer errors [16]. Now, CT image analysis programs have

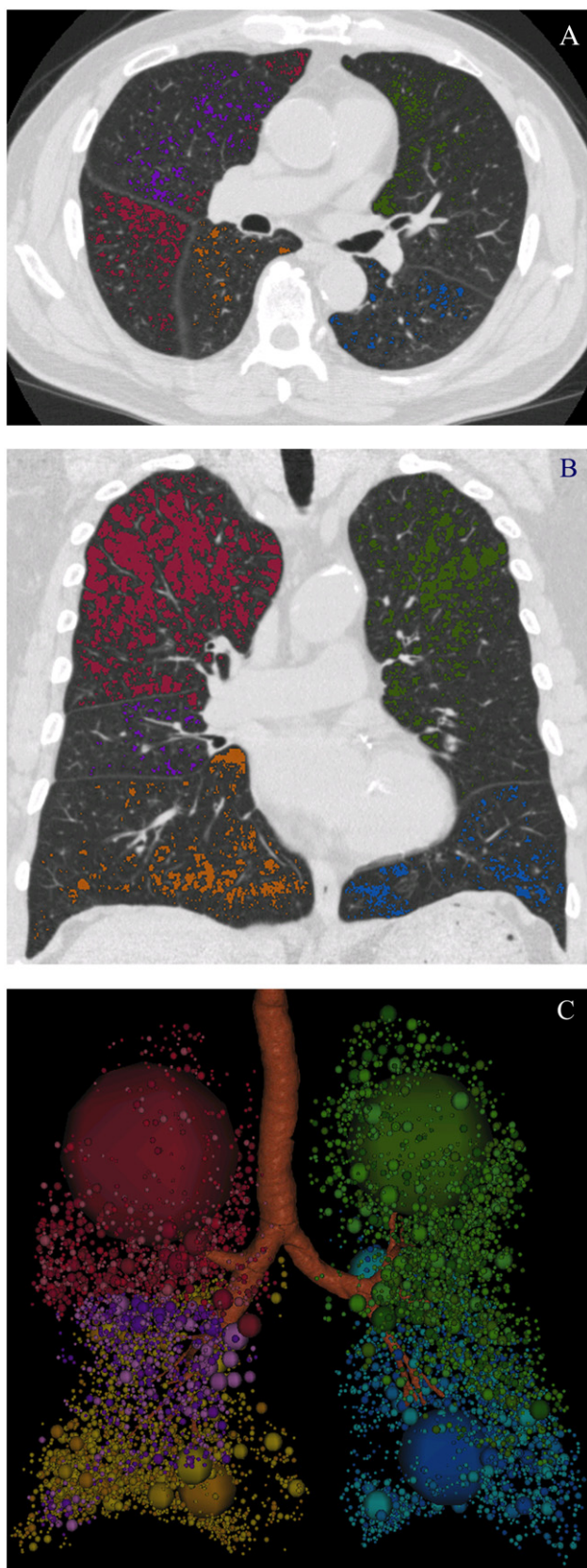
been developed to segment the lung parenchyma and measure lung density on CT images. The extent of emphysema quantified using these programs is based on threshold cut-off methods, also known as density mask [14,17–19] or percentile point methods [20–25]. The “density mask” method is used more often. This method uses overlay masks to distinguish the location and size of emphysematous lesions on the CT images (Fig. 1). With this method, LAA is defined as the total number of pixels (for 2-dimensional images) or voxels (for 3-dimensional images) that demonstrate lung attenuation below a certain threshold [19] that is predetermined in accordance with lung volume at scanning, slice thickness, and reconstruction algorithms and can range from –856 HU to –960 HU [14,17–19]. LAA% quantified by these methods correlates well with the extent of emphysema quantified by visual scoring systems [19,26] and macroscopic [16,17,19,25] and microscopic measurements [18,25]. Because LAA% is affected by CT machine calibration [27], lung volume at scanning [24,28–30], reconstruction slice thickness [22], and reconstruction algorithm [31], these factors should be controlled for valid results in longitudinal studies.

LAA% quantified on CT scans at full inspiration is associated with forced expiratory volume in 1 s ( $FEV_1$ ), ratio of  $FEV_1$  to forced vital capacity ( $FEV_1/FVC$ ), residual volume (RV), *diffusing capacity of the lung for carbon monoxide* ( $D_{LCO}$ ), and ratio of  $D_{LCO}$  to alveolar volume ( $D_{LCO}/VA$ ) [32–37]. These relationships reflect the contribution of emphysema to airflow limitation and reduced diffusing capacity in COPD. LAA% can be estimated from a model that includes  $FEV_1$  and  $D_{LCO}/VA$  [34,35]. Some investigators have also shown that LAA% quantified at full expiration correlated more closely with pulmonary function tests, especially with RV/total lung capacity (TLC), which reflects air trapping in COPD, than LAA% quantified at full inspiration [32,38–42]. They argue that LAA% quantified at full expiration reflects both air trapping and emphysema in COPD. Nonetheless, because lung CT scans are generally performed at full inspiration in routine practice, in most ongoing studies, LAA% is still quantified at full inspiration rather than at full expiration.

Clinically, LAA% is higher in males than in females [43,44], and it increases with increasing age and number of pack-years of smoking [44]. LAA% correlates negatively with body mass index (BMI) [45–47] and positively with degree of dyspnea [33]. Furthermore, LAA% complements  $FEV_1$  in explaining the severity of dyspnea [48].

Emphysema quantification has been applied to longitudinal studies as well as cross-sectional studies. In 144 patients with COPD who were followed for 30 months, detection of emphysema progression was found to be 2.5-fold more

sensitive with lung densitometry than by  $FEV_1$  or gas diffusion [49]. In another study, 60 patients with COPD were prospectively monitored for exacerbations for 2 years. The



annual increase in LAA% was significantly greater in patients with exacerbations than in patients without exacerbations ( $P < 0.0001$ ), while there was no difference in the  $FEV_1\%$  decline between the 2 groups ( $P = 0.40$ ) [50]. A greater extent of emphysema at baseline CT scanning was associated with higher rates of lung function decline in obstructed and non-obstructed smokers after 3 years of follow up. The extent of emphysema at baseline CT scanning also helped to identify non-obstructed smokers who were predicted to develop air-flow obstructions [51].

Emphysema assessment by quantitative CT is a good predictor of mortality in COPD patients. A higher LAA% has been associated with increased mortality from respiratory diseases [52]. In addition, emphysema can be a predictor of comorbidity in patients with COPD. LAA% has been correlated with bone mineral density of the thoracic vertebrae as measured by CT densitometry [53]. The presence of visual or quantitative emphysema is associated with osteoporosis of the lumbar and hip bones detected by dual-energy X-ray absorptiometry [54]. The presence of emphysema assessed using a visual scoring system is also associated with lung cancer in smokers. This association remains significant after adjusting for age, sex, smoking history, and level of airflow limitation [55–57]. Emphysema severity is also associated with arterial stiffness, a marker of cardiovascular risk. This association is independent of age, sex, smoking history, airflow limitation, or systemic inflammation [58,59].

The extent of emphysema is quantified for the whole lung and for lung regions such as core (inner) versus rind (outer) regions [37,60], upper versus lower regions [60], or even for each lobe within the lung [61]. This application of quantitative CT helps in selecting candidates for lung volume reduction surgery (LVRS) and provides insights into the mechanisms of improvement after LVRS. In a subgroup of 21 patients with severe COPD who underwent LVRS, post-operative changes in  $FEV_1$  and maximal exercise capacity correlated with extent of preoperative emphysema of the whole lung [60,62,63] and the upper [62], and upper-rind regions of the lungs [60]. The volume reduction in regions with severe emphysema [63] or with confluent emphysema [62] has been cited as a mechanism of improvement after LVRS. However, with multiple regression analysis, only the extent of emphysema of the upper-rind region of the lungs was a significant predictor for improvement of pulmonary

**Fig. 1 – Quantification of emphysema using the density mask method.** Emphysematous lesions are masked with different colors depending on the pulmonary lobes (red for right upper lobe, purple for right middle lobe, dark yellow for right lower lobe, green for left upper lobe, and blue for left lower lobe). (A) Axial section image. (B) Coronal section image. (C) Three-dimensional image, with the spheres representing the sizes of the emphysematous lesions. These images were obtained from a 79-year-old male patient with stage III COPD using Pulmonary Workstation 2.0 (VIDA Diagnostics, IA, USA) and reconstructed with 1-mm slice thickness and a standard algorithm. The threshold cut-off for emphysema was  $-950$  HU. The percentage of low attenuation area (LAA%) in this patient was 15%.



function after LVRS [60]. This result was repeated in a recent study with 546 patients [64]. However, the magnitude of these correlations was very small ( $R^2=0.15$  for prediction of FEV<sub>1</sub> change and  $R^2=0.16$  for prediction of maximal capacity change), which has raised concerns about the clinical application of the result.

Besides the values of quantitative CT for patients with COPD, we should also be aware of the risk of radiation exposure. Because of the concern that repeated CT scans over time may be associated with consequent cancer risk [65], several investigators have proposed low-dose CT scans (30–60 mA s) as an alternative to standard-dose CT scans (100–250 mA s) in the quantification of emphysema. They found that even though the mean noise level was greater with low-dose than with standard-dose CT, there was a good correlation of LAA% between the 2 protocols [66,67]. At most thresholds of emphysema, the LAA% was greater on low-dose than on standard-dose scans [22,66], but the difference might not be clinically important [66]. However, because the effect of radiation dose on LAA% varies depending on lung volume [68] and slice thickness [22], these 2 factors should be taken into account when comparing LAA% between scans with different radiation doses.

In summary, the extent of emphysema as determined by quantitative CT correlates with macroscopic and microscopic measurements of emphysema, pulmonary function tests, and clinical symptoms. Emphysema evaluation using quantitative CT has been applied for selecting candidates for LVRS or for phenotyping COPD patients for ongoing studies, which we will discuss in the final section of this review.

### 3. Quantification of airway dimensions

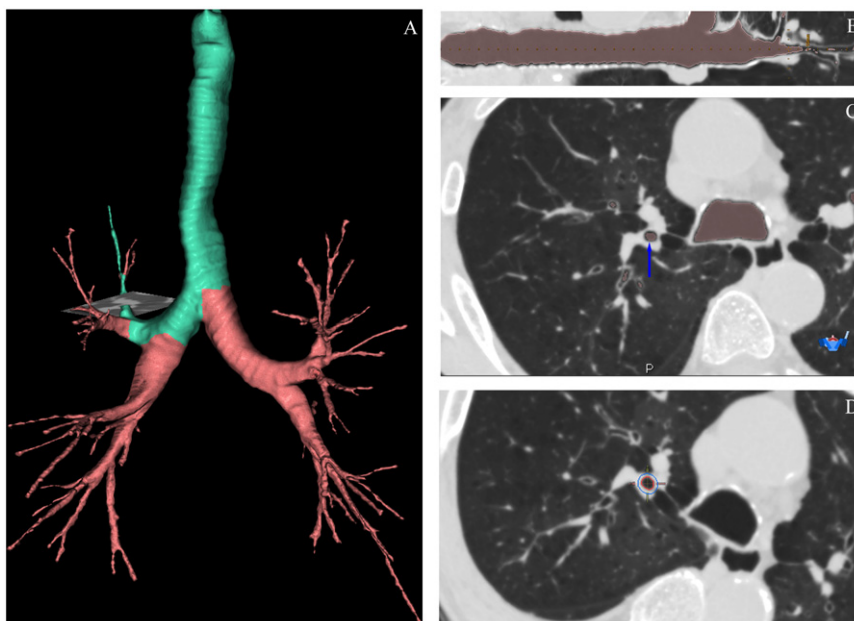
Quantification of airway dimensions in COPD is used to evaluate airway wall thickening and lumen narrowing. The severity of these histologic changes correlates with the severity of COPD evaluated according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [4]. Therefore, several CT image analysis programs have been developed to measure airway internal area ( $A_i$ ) and airway wall area ( $A_{aw}$ ) on CT images. Further indexes of airway dimensions including airway outer area ( $A_o$ ) ( $A_o=A_i+A_{aw}$ ) and the percentage of wall area (WA%) [ $WA\%=(A_{aw}/A_o) \times 100$ ] can also be derived from these measurements. The algorithm for detecting airway lumen is based on the density mask method, and threshold values for airway lumen vary from –500 HU to –577 HU [69]. Algorithms for detecting the inner and outer margins of airway walls are based on different methods including full-width at half-maximum [36,70], maximum-likelihood [71], score-guided erosion [69], Laplacian of Gaussian [72], and fitting ellipses [73]. These programs have been validated in phantom studies and in excised pig, sheep, and human lungs by micrometer measurements and manual estimation [69,72–74]. Initially, these programs were limited to quantifying the dimensions of airways with ratios of longest-to-shortest diameters of less than 2.0 on 2-dimensional CT images [36,72,75,76]. This limitation was intended to avoid underestimating  $A_i$  and overestimating  $A_{aw}$ , especially for small airways [69,71]. However, it reduces

the count of measurable airways on each CT image or the whole lung [73]. Since the advent of multi-slice CT scanners and volumetric CT scanning methods, the bronchial tree can now be reconstructed using 3-dimensional CT analysis programs. These programs can be applied to measure the airway dimensions of nearly all visible airways at specific locations, even those that are not oriented perpendicularly to the axial plane (Fig. 2) [73,74,77–80].

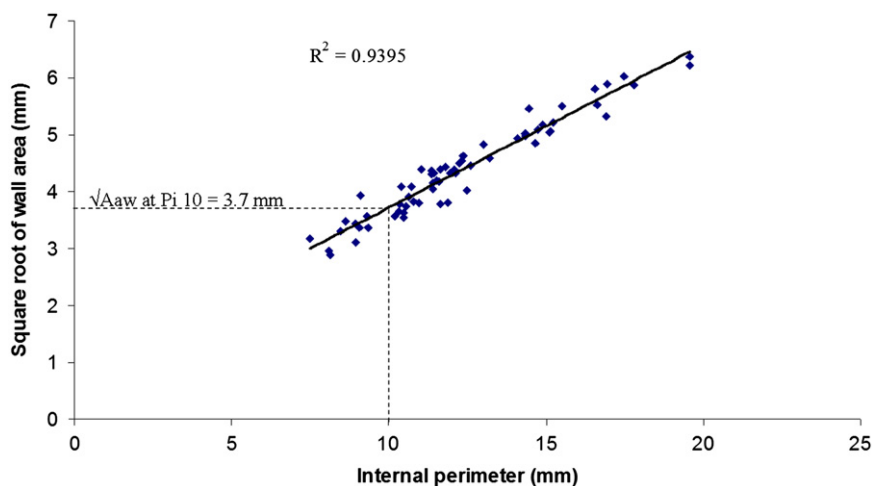
Initially, due to limitations of CT resolution and analysis programs [36,81,82], only segmental bronchi (third generation) were evaluated. Presently, bronchi up to the 6th generation have been measured in patients with COPD using CT analysis programs [74,77,78]. Even though these measured locations are not at the site of obstruction in COPD [4], the correlation between airway wall areas of relatively large airways measured by CT and those of small airways measured by histology analysis has justified these evaluations in COPD [75]. The strong correlation of airway dimensions obtained using CT and optical coherent tomography further supports the usefulness of quantitative CT in the determination of airway dimensions [83]. However, to date, no consensus has been reached about locations and counts of measurable airways for quantification of airway dimensions in COPD. Some investigators evaluate only the apical bronchus of the right upper lobe [36] because airway dimensions at this location correlate with those at the basal bronchus of the right lower lobe [82], and both are perpendicular to axial CT sections. However, because the WA% of the anterior basal segmental bronchus of the right lower lobe correlates with FEV<sub>1</sub> more closely than that of the apical segmental bronchus of the right upper lobe [77], others have measured representative bronchi for each lobe [70,81,84,85], or even as many bronchi as possible [76,78,86,87]. When measuring airway dimensions at different locations along each bronchus and/or along different bronchi, the mean or median of all these measurements is estimated to provide values for each subject [76,78,86]. However, this method neglects the heterogeneity of airway dimensions between generations along each bronchus [70,77,88] or between different lobes in patients with COPD. To solve this problem and to generate comparable results in cross-sectional or longitudinal studies, the square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm ( $\sqrt{A_{aw}}$  at Pi10) has emerged (Fig. 3) [75]. This index of airway dimensions correlates with pulmonary function tests and clinical symptoms [48,81,87].

WA%,  $A_i$ , and  $\sqrt{A_{aw}}$  at Pi10 are common indexes of airway dimensions, and have been used in many studies relating to COPD. WA% and  $\sqrt{A_{aw}}$  at Pi10 represent airway wall thickening or remodeling.  $A_i$  represents lumen narrowing due to airway wall thickening, luminal inflammatory exudates, and/or loss of parenchymal tethering in patients with COPD. WA% [36,70,77,86],  $A_i$  [70,77,84], and  $\sqrt{A_{aw}}$  at Pi10 [87] have all been correlated with FEV<sub>1</sub>. The correlation coefficients of WA% or  $A_i$  with FEV<sub>1</sub> increase as the bronchial size decreases from the third to the sixth generation of bronchi [70,77,84].

In addition to the parameters of pulmonary function tests, airway dimensions also correlate with clinical symptoms in patients with COPD. Patients with symptoms of chronic bronchitis are more likely to have higher WA% or  $\sqrt{A_{aw}}$  at



**Fig. 2 – Quantification of airway dimensions using a 3-dimensional CT analysis program. (A)** The bronchial tree and the pathway of the target airway (in green color) with the location of measurement (gray horizontal plane). **(B)** Curved multi-planar reconstruction image of the target airway and the location of measurement (vertical dashed yellow line). **(C)** An axial section with airway lumen is masked in pink and the blue arrow indicates the measured bronchus. **(D)** The inner and outer margins of the measured bronchus are marked as red and blue circles, respectively. These images were obtained from a 75-year-old male patient with stage IV COPD using Apollo 1.1 (VIDA Diagnostics, IA, USA).



**Fig. 3 – Estimation of  $\sqrt{A_{wa}}$  at Pi10.** The square root of the wall area of the measured segment is plotted against its internal perimeter. The square root of the wall area of the hypothetical airway with an internal perimeter of 10 mm ( $\sqrt{A_{wa}}$  at Pi10) is calculated from the linear regression equation. This figure shows the  $\sqrt{A_{wa}}$  at Pi10 of the patient in Fig. 2 calculated from all measured bronchial segments with internal perimeters ranging from 6 to 20 mm. The  $\sqrt{A_{wa}}$  at Pi10 was 3.7 mm and the  $R^2$  value of the linear regression equation was 0.94.

Pi10 than patients without these symptoms [48,76,81]. WA% in patients with COPD is lower than that in patients with asthma [85], but higher than that in healthy smokers [36] and non-smokers [86].  $\sqrt{A_{wa}}$  at Pi10 decreases with increasing age, increases with increasing number of pack-years of smoking, and is higher in males than in females, even after adjusting for FEV<sub>1</sub> [44].

Very few longitudinal studies have reported quantification of airway dimensions. In one study, during 4 years of follow-up of

38 patients with COPD, annual changes in WA% were inversely correlated with annual changes in FEV<sub>1</sub> ( $r = -0.363$ ,  $P = 0.025$ ) [89]. More findings relating to this aspect of airway dimensions are expected when results of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) [90] and other longitudinal studies are reported in the near future. Regarding changes in airway dimensions in response to specific treatment, the relationship of changes between Ai and FEV<sub>1</sub> in response to a 7-day course of tiotropium bromide

inhalation in 15 patients with COPD was investigated. The mean percentage Ai increase was correlated with percent FEV<sub>1</sub> increase ( $r=0.843$ ,  $P<0.001$ ). Such correlations were significant for the fourth to sixth generation bronchi, but not among the third generation bronchi [91].

In summary, WA% and  $\sqrt{Aaw}$  at Pi10 are useful investigative parameters because they reflect airway wall remodeling and are associated with levels of airflow limitation and clinical symptoms in patients with COPD. However, further studies are still needed to standardize measurements and clarify the implications of quantification of airway dimensions in COPD.

#### 4. Quantification of small pulmonary vessels

In addition to evaluation of emphysema and airway dimensions, quantitative CT is applied to quantify small pulmonary vessels in COPD. Matsuoka et al. used a semi-automated CT analysis program to segment pulmonary vessels on 2-dimensional CT scans [92–94]. The total cross-sectional area of small pulmonary vessels (CSA), including subsegmental vessels (those with cross-sectional area from 5 to 10 mm<sup>2</sup>, CSA<sub>5–10</sub>) and subsegmental vessels (those with cross-sectional area less 5 mm<sup>2</sup>, CSA<sub><5</sub>), was calculated from selected CT images. The percentage of total CSA to the corresponding lung area (%CSA<sub>5–10</sub>, %CSA<sub><5</sub>, respectively) was generated and correlated other indices. In smokers, %CSA<sub><5</sub> was significantly correlated with LAA% ( $r=-0.83$ ,  $P<0.0001$ ), FEV<sub>1</sub>% predicted ( $r=0.29$ ,  $P<0.0001$ ), and FEV<sub>1</sub>/FVC ( $r=0.45$ ,  $P<0.0001$ ) [92]. In patients with COPD, %CSA<sub><5</sub> was negatively correlated with pulmonary arterial mean pressure [93] and thoracic aorta calcification score [94]. These findings implied that a reduction in CSA is associated with increased degrees of emphysema, pulmonary hypertension, and atherosclerosis in COPD.

Contrary to %CSA<sub><5</sub>, there was no significant correlation or only a weak correlation between %CSA<sub>5–10</sub> and the other aforementioned indices in COPD. This finding supports the notion that alterations in pulmonary vasculature may occur predominantly in peripheral vessels [92–94].

Evaluation of small pulmonary vessels using quantitative CT currently has the following limitations: firstly, small pulmonary arteries and veins are not evaluated separately. Secondly, CSA measurements are affected by several factors, including cardiac cycle, respiratory cycle, and scanning protocol. Thirdly, thus far, there are no standard CT scanning protocols or fully-automated CT image analysis programs that have been validated to accurately quantify small pulmonary vessels.

In summary, evaluation of small pulmonary vessels using quantitative CT can reflect pulmonary vascular changes in COPD patients, but research is still needed in order to certify the utility of quantitative CT as a non-invasive tool for assessing pulmonary arterial hypertension and other morphological changes in small pulmonary vessels in patients with COPD.

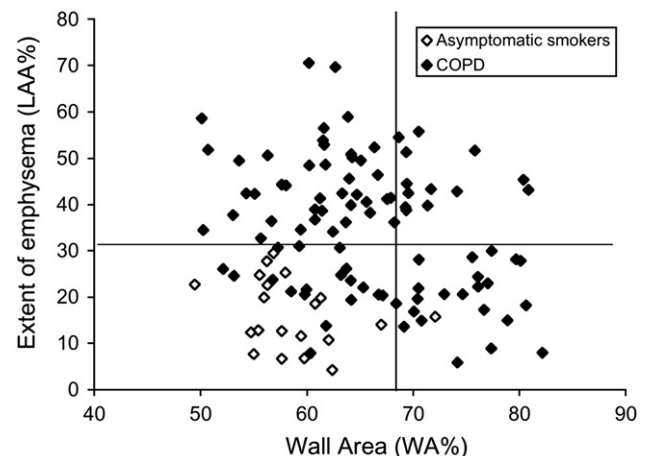
#### 5. COPD phenotypes

The GOLD guidelines for the diagnosis and management of COPD are mainly based on FEV<sub>1</sub>% predicted and are useful to

classify disease severity and choose a corresponding treatment regimen [3]. However, even within the same GOLD stage, patients with COPD will present with different clinical subtypes depending on BMI, severity of dyspnea, frequency of acute exacerbations, and response to inhaled corticosteroids (ICS) or bronchodilators [95–97]. With each subtype, it is important to choose an appropriate regimen in order to optimize the cost-effectiveness of the chosen treatment. If there is no means other than FEV<sub>1</sub> for classifying patients with COPD into specific groups in longitudinal studies, the effects of certain treatments may not be proved in terms of primary outcomes [98]. Phenotyping COPD patients based on quantitative CT findings has partly addressed this concern.

##### 5.1. Airway remodeling-dominant versus emphysema-dominant phenotypes

Patients with COPD can be divided into 3 groups on the basis of WA% and LAA%: an airway remodeling-dominant group (high WA% and low LAA%), an emphysema-dominant group (low WA% and high LAA%), and a mixed group (high WA% and high LAA%) (Fig. 4) [99]. From this point of view, several investigators have tried to phenotype COPD according to quantitative CT in order to relate these phenotypes to clinical symptoms and pulmonary function tests. Patients with symptoms of chronic bronchitis had lower LAA% and higher WA% than patients without symptoms [76]. Meanwhile, patients with the airway remodeling-dominant phenotype had significantly higher BMI, increased wheezing, and better response to bronchodilators or ICS than those with the emphysema-dominant or mixed phenotype [96,97]. Patients



**Fig. 4 – Phenotypes of COPD based on quantitative CT. Relationship between percentage of wall area (WA%) and percentage of low attenuation area (LAA%) in 94 patients with COPD and 20 asymptomatic smokers. The horizontal line represents the mean +2SD of LAA% of the asymptomatic smokers. The vertical line indicates the mean +2SD of WA% of the asymptomatic smokers. Using these cut-off values, patients with COPD can be divided into 3 groups: an airway remodeling-dominant group (high WA% and low LAA%), an emphysema-dominant group (low WA% and high LAA%), and a mixed group (high WA% and high LAA%). Adapted from Nakano et al. [99].**

with the emphysema-dominant phenotype showed minimal reversibility in response to treatment with bronchodilators or ICS [96,97,100,101]. It is possible that phenotyping COPD based on quantitative CT analysis may open new avenues of pharmaceutical research for COPD, possibly facilitating development of drugs that target the airway wall remodeling process or the alveolar destruction process [102]. This method also helps to classify patients with COPD into appropriate subgroups for interventional trials, and should complement pulmonary function tests in objective evaluation of outcomes for those trials while recognizing potential benefits of specific regimens tailored to the subgroups.

## 5.2. Phenotypes of COPD based on quantitative CT for genotypic studies

The genetic component plays a significant role in the pathogenesis of COPD, which explains why only 15–20% of smokers develop COPD and why COPD patients of varying ethnicities, genders, and risk factors have different clinical phenotypes [3]. Determining which genes are responsible for predisposition to COPD or which genes determine specific phenotypes might prove crucial for rigorous prevention, early detection, and potential cure.

Reproducible COPD phenotypes defined by quantitative CT can facilitate investigations of genotypes because of the similar pathogenic mechanisms represented by each phenotype. The role of genetic control in developing COPD was highlighted in a study of 519 probands and 640 siblings. The results showed that emphysema was more prevalent in the siblings of probands with significant emphysema than in the siblings of probands without emphysema.  $\sqrt{\text{Aaw}}$  at Pi10 in the siblings was significantly correlated with those of the probands [87].

Genetic predisposition to emphysema has been investigated in several studies. A group-specific component of serum globulin (Gc-globulin) polymorphism has been significantly associated with susceptibility to COPD and with the severity of emphysema in a Japanese population [103]. By using a genome-wide association study (GWAS) method to identify genetic determinants of emphysema in Caucasian patients with COPD investigators identified *BICD1* [104] and *CHRNA3/5* [105] as novel genes for emphysema susceptibility in COPD. Matrix Metalloproteinase-9 (MMP-9) polymorphism was also thought to be related to emphysema, but ultimately this was not proven [106,107] although it was associated with upper lung-dominant emphysema in Japanese patients with COPD [107]. Apical-predominant emphysema also appeared to be influenced by various genes including *GSTP1*, *EPHX1*, and certain *MMP1* polymorphisms of xenobiotic metabolizing enzymes in Caucasians with COPD [108], and other genes have been associated with protective mechanisms against emphysema. For example, Japanese patients with COPD who had the –28G allele of the *CCL5* gene had findings associated with milder emphysema [109]. For Caucasian populations, smokers with a less active form of *MMP-12* may be partly protected from severe emphysema [110].

Because there is no optimal method of quantifying airway dimensions yet, there have been very few studies investigating genotypes of the COPD patients with airway remodeling-dominant phenotypes. One study in 111 patients with COPD in a South Korean population measured airway dimensions near

the origins of the right apical segmental bronchus and the left apical-posterior segmental bronchus, and investigators found that the *ADRB2* genotype with a G allele was associated with the airway remodeling-dominant phenotype [111]. Another study was conducted to identify the association between 3 loci (*HHIP*, *FAM13A*, *CHRNA3/5*) and COPD phenotypes in 1609 Caucasian patients with COPD. Airway wall thickness measurements ( $\sqrt{\text{Aawa}}$  at Pi10 and WA%) were not associated with any of these single nucleotide polymorphisms [105].

In summary, the utility of phenotyping COPD patients for further interventional and genotypic studies has become more apparent. Reproducible phenotypes of COPD based on quantitative CT have partly met the demand.

## 6. Conclusions

CT technology and CT image analysis programs have improved over time so that quantitative CT studies for COPD patients are less time-consuming, more convenient, and more reproducible. These improvements have led to new findings related to extent of emphysema, airway dimensions, and condition of the small pulmonary vessels that have been described in recent years. Phenotyping of COPD based on quantitative CT has facilitated interventional and genotypic studies. Minimizing radiation exposure, controlling the uniformity of CT scanning parameters, and standardizing the quantification of airway dimensions and small pulmonary vessels should be considered. More studies are needed to address the current limitations of quantitative CT. We anticipate that quantitative CT for COPD will be useful not only in research, but also in routine clinical practice.

## Conflict of interest

Division of Respiratory Medicine, Department of Medicine, Shiga University of Medical Science received a research Grant from Otsuka Pharmaceutical Co., Ltd.

Yasutaka Nakano received lecture fees from Nippon Boehringer Ingelheim Co., Ltd.

Nguyen Van Tho, Hiroshi Wada, Emiko Ogawa, they have no potential conflict of interest.

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