Computed tomography-identified phenotypes of small airway obstructions in chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characteristic of small airway inflammation, obstruction, and emphysema. It is well known that spirometry alone cannot differentiate each separate component. Computed tomography (CT) is widely used to determine the extent of emphysema and small airway involvement in COPD. Compared with the pulmonary function test, small airway CT phenotypes can accurately reflect disease severity in patients with COPD, which is conducive to improving the prognosis of this disease. CT measurement of central airway morphology has been applied in clinical, epidemiologic, and genetic investigations as an inference of the presence and severity of small airway disease. This review will focus on presenting the current knowledge and methodologies in chest CT that aid in identifying discrete COPD phenotypes.

Keywords: Chronic obstructive pulmonary disease; Small airway obstruction; Computed tomography; Phenotype; Pulmonary function test

Introduction

Chronic obstructive pulmonary disease (COPD) is a common and frequently occurring disease of the respiratory system. Its primary clinical features are persistent airflow limitations, persistent respiratory disease symptoms, high morbidity, disability, and mortality, all of which can seriously affect the quality of life in patients with COPD;[1] additionally, it is also one of the leading causes of death worldwide.[2] The diagnosis and treatment of COPD are rapidly changing; hence, a better understanding of recent advances is important for delivering optimal patient care.[3]

Spirometry is the reference gold standard for diagnosing COPD and assessing disease severity. Spirometry-defined and -diagnosed COPD is highly prevalent in the adult population of China. Cigarette smoking, ambient air pollution, being underweight, previous childhood chronic cough, lower levels of education, and a parental history of respiratory diseases are the major risk factors for COPD.[4] These can often result in the irreversible destruction of lung tissue (emphysema) and inflammation, remodeling of small airways, or both. Although COPD is diagnosed and staged with a pulmonary function test (PFT), computed tomography (CT) enables quantification of abnormal changes in the lung parenchyma.[5]

COPD is often caused by continuous inhalation of toxic particles and gases, with most patients displaying a history of tobacco inhalation.[6] Recent research indicated that among individuals aged < 50 years with ≥ 10 pack-years of tobacco consumption, 15% fulfil the criteria for early COPD. Individuals with early COPD more often have chronic respiratory symptoms and lung function impairment; this is alongside an increased risk of acute exacerbation, hospitalizations, and early death.[7]

Continuous damage in the lungs recruits local inflammatory immune cells, resulting in the formation of abnormal scar tissue that affects the morphology of lung tissue.[8]

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This damage, in turn, can alter the respiratory function of the lungs to varying degrees. In different parts of the lung tissue, the immune response can be inconsistent, resulting in varying degrees of damage.[9] The main disease manifestations are chronic bronchial inflammation, enlargement of the bronchial mucous glands, and goblet metaplasia of the airway endothelium.[10]

Insufficiency of PFT in Assessing COPD Severity

The PFT, a convenient manipulatory technique, provides direct measurement for monitoring the progression and severity of COPD.[11] Different individuals have different pathophysiological processes. Significant heterogeneity exists in patients with COPD regarding clinical manifestations and disease progression.[12] However, accumulating studies have shown that lung function results are similar in patients with varying degrees of COPD. While there are differences in clinical symptoms and test indicators, PFT cannot accurately explain an individual patient's situation.

Lung function decreases progressively in COPD. To some extent, the forced expiratory volume in 1 s (FEV_1) can reflect both the severity and complexity of lung function. However, in actuality, FEV_1 alone cannot address the severity and complexity of the disease. Hence, FEV_1 cannot be used as an ideal indicator for the diagnosis, evaluation, and treatment of COPD.[13] A mean forced expiratory flow between 25% and 75% (FEF25-75) is considered as the most sensitive measurement of airflow in peripheral airways representative of airflow obstruction, which is reduced in early bronchial impairment in association with small airway disease (SAD).[14] Of note, FEF25-75 also includes large airway flow. Imaging can directly display the structure of lung tissue, thus characterizing COPD and reflecting different states of lung tissue among different individuals. As treatments have become more personalized, imaging may be a unique way to understand what COPD actually looks like [Figure 1].

Anatomical Features and Physiological Characteristics of Small Airways

Bronchioles are designated as bronchial tubes lacking mucous glands and cartilage. Bronchioles account for the majority of small airways. Clinically, small airways are usually located in the eighth grade respiratory bronchus, which comprises almost all (98.8%, approximately 4500 mL) of the total lung volume.[15] The inner diameter of the small airway lumen is less than 2 mm. The minimum diameter can reach approximately 0.06 mm after continuous branching.[16]

Since small airways have no cartilaginous support, they are more easily affected by pressure changes in the thoracic cavity.[17] Approximately 80% of respiratory resistance in the lungs comes from large airways, whereas only 20% of resistance comes from small airways.[18] Following the combined action of both neural and humoral regulation, small airway smooth muscles can relax and contract, altering the airway diameter, and subsequently controlling gas exchange.

Pathological Changes in Small Airways in COPD

SAD, a cardinal feature of COPD, was first recognized in the 19th century. Airway epithelial cells are the first barrier to harmful gases and particles, which are present in the small airways. After exposure to harmful substances, the local inflammatory reaction is upregulated, thereby inducing morphological changes in airways [Figure 2].[19]

COPD is caused by continuous inhalation of toxic particles, gases, and pathogens that induce respiratory tract infections; however, most cases are related to tobacco inhalation. Small airways are narrowed as the airway wall is thickened as a result of inflammation. In response, aberrant repair processes result in distal hypoventilation, air entrapment, and low blood flow. In addition, the lumen is occupied by tenacious mucus as a result of goblet hyperplasia, mucus hypersecretion, and impaired mucociliary clearance. These contribute to the onset and progression of small airways disease. This can affect the respiratory function of the lungs to varying degrees and can reduce lung cross-sectional area, thus increasing the risk of lung failure. CT images can demonstrate different signs: limited ground glass, shadow of center nodule with blurred edges, tree-in-bud sign, local density reduction area or mosaic perfusion, etc.

The diverse histopathological features associated with SAD underpin the heterogeneous nature of COPD. Previously, studies have described small airway abnormalities in COPD as inflammation, fibrosis, and mucus blockages, which are related to the severity of airflow obstruction. Hogg *et al*[20] discovered that the thickening of airway walls was closely related to the repair of inner wall damage. Moreover, the degree of lumen obstruction and inflammatory response were weakly correlated with the progression and prognosis of COPD.

McDonough *et al*[21] selected multi-slice spiral CT images of 78 patients with COPD, in which the bronchus structure can be clearly displayed, and judged by scoring on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) scale. The comparative results showed fewer small airways in GOLD stage 1 patients, which were further reduced in GOLD stage 3 and GOLD stage 4 patients. In fact, during the comparison process, researchers raised doubts regarding the reduced number of small airways, as they were unsure whether these small airways had narrowed without detection or even disappeared.

Current data suggest that the inflammatory response in small airways might precede fibrosis and remodel the lung tissue; furthermore, it may result in a clinically detectable decline in lung function.[22-24] Bhatt *et al*[25] detected pulmonary inflammatory responses in smokers and nonsmokers, showing increased $CD8^+$ T lymphocytes in the large airways, small airways, and parenchyma of smokers. Meanwhile, these $CD8^+$ T lymphocytes induced apoptosis and necrosis of epithelial and endothelial cells in the lungs; however, the number of inflammatory cells was unrelated to the intensity of smoking.

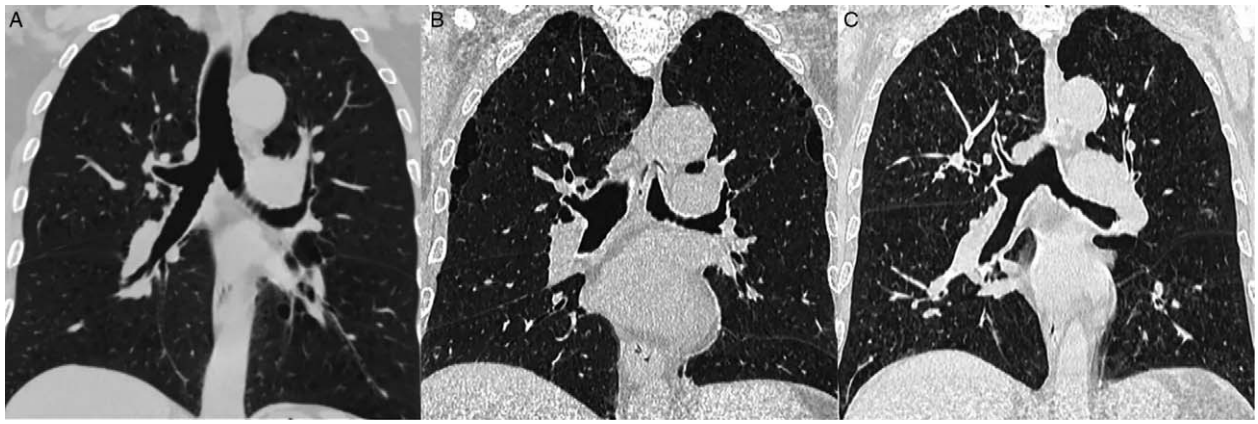

Figure 1: Coronal CT images of three patients with varying degrees of small airway disease. (A) A 64-year-old male with 56 pack-years, FEV_1 96% predicted, FEV_1/FVC 102%, RV/TLC 95% predicted, and DLCO 95% predicted. This patient showed normal lung function with air trapping. (B) A 69-year-old male with 72 pack-years, FEV_1 90% predicted, FEV_1/FVC 85%, RV/TLC 117% predicted, and DLCO 75% predicted. This patient was diagnosed with chronic bronchitis, emphysema, and bullae, accompanied by evident air trapping. (C) A 70-year-old male with 35 pack-years and COPD GOLD stage 3, FEV_1 60% predicted, FEV_1/FVC 58%, RV/TLC 166% predicted, and DLCO 85% predicted. This patient showed predominantly functional small airway disease in both lungs. COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; DLCO: Diffusing capacity of the lung for carbon monoxide; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; RV: Residual volume; TLC: Total lung capacity.

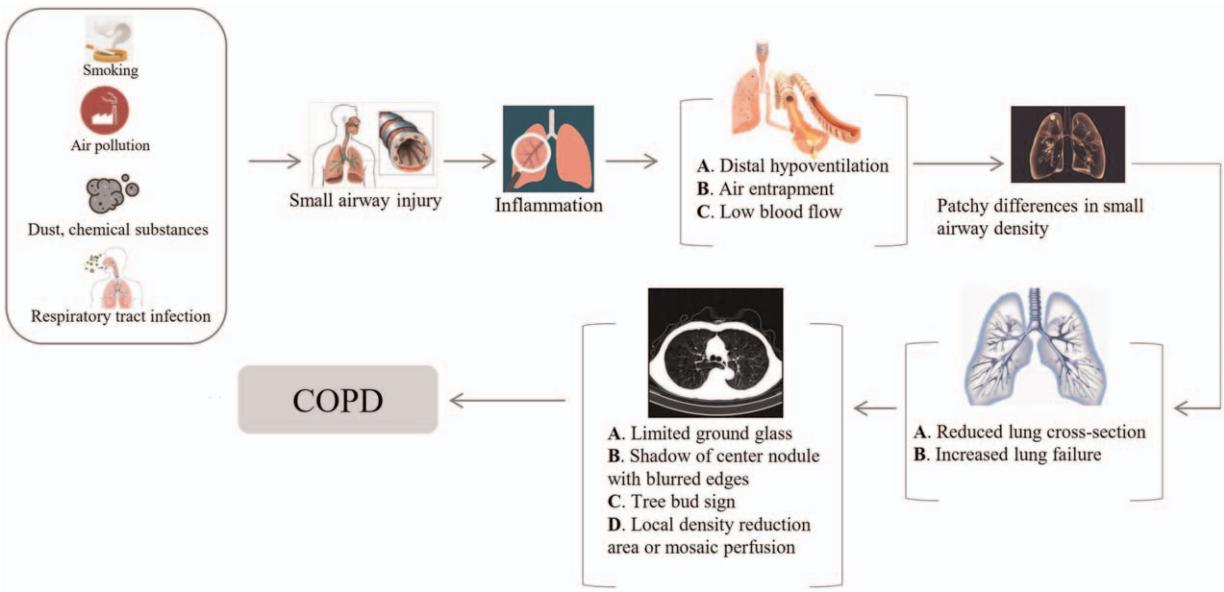

Figure 2: Main mechanism of small airway disease onset and progression of chronic obstructive pulmonary disease (COPD).

Overview of COPD phenotypes

Typically, phenotypes are specific appearances or components of an object in a lifetime, influenced primarily by both the host's genotype and environment. Phenotyping is designated to identify patients with unique prognostic or therapeutic characteristics. In the research fields of COPD, identifying phenotypes, including symptoms, imaging, physiology, and molecular biology, has become an important venture.[26] Phenotypes facilitate a better understanding of disease evolution, punctuated by exacerbations; moreover, they can aid in favoring a series of potential targets for clinical translation.[27,28] With in-depth interpretation of COPD phenotypes, heterogeneity will be deciphered, bringing about new strategies for COPD diagnosis and treatment.

CT-identified Phenotypes of Small Airway Obstructions in Patients with COPD

Data analysis, based on chest CT scans, can quantify airway wall changes and emphysema severity, thus dividing patients with COPD into three main types, including those with symptoms of emphysema, airway changes, or both. After these divisions, they can then be further divided into different sub-types.[29] The major sites of obstruction lie within the small conducting airways in COPD. CT is currently the preferred method for obtaining lung morphology images in patients with COPD.[30] As a minimally invasive imaging technique, CT scanning is capable of providing high-contrast and high-resolution details of the lungs and airways.

Table 1: Main CT small airway phenotypes in COPD.

Phenotype	Target	Parameters	Objectives
Functional phenotypes of HRCT	Emphysema	LAA-950 HU	Quantify the degree of emphysema
	Gas trapping	LAA-856 or LAA-850 HU	Investigate the association between gas trapping and lung function decline and RV
	Thickness of airway wall or intraluminal area	Wall area% Pi10	Investigate the association between thickness of airway wall and acute exacerbation rate and the severity of airflow obstruction
Parametric response mapping	Emphysema	PRM_{emph}	Distinguish the relative contributions of fSAD and emphysema
	Gas trapping	PRM_{fSAD}	Detect terminal bronchioles loss, luminal narrowing, and obstruction
Ventilatory function phenotype	Ventilation function and emphysema	Xenon gas ventilation map MDIs	Determine the etiology of airflow limitation
Micro-CT phenotype	Total number of terminal bronchioles and emphysema	Preterminal bronchiolar length, wall thickness, lumen circularity, and number of alveoli	Detect loss of terminal bronchioles early in small airway

COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; fSAD: Functional small airways disease; HRCT: High resolution computed tomography; HU: Hounsfield unit; LAA: Low attenuation area; LAA-950: Low attenuation lung area below −950 Hounsfield units; LAA-856: Low attenuation lung area below −856 Hounsfield units; LAA-850: Low attenuation lung area below −850 Hounsfield units; MDIs: Material decomposition images; Pi10: Internal perimeter of 10 mm; PRM: Parametric response mapping; PRM_{emph}: Emphysema on parametric response mapping; PRM_{fSAD}: Functional small airways disease on parametric response mapping; RV: Residual volume.

Chest CT morphological manifestations allow the thickening of airway walls, emphysema, and trapped air in patients with COPD to be detected and measured in clinic.[31] Notably, the CT emphysema phenotype study can be conducted to explore the pathogenesis of COPD. Collectively, these associations between different sub-types and specific clinical manifestations support the definition of COPD phenotypes.[32]

Upon comparing the CT scans of small airways at different stages of COPD, it was found that stenosis and occlusion of the small airway occur earlier than emphysema or the gradual increase in peripheral airway resistance. This suggests that CT examinations can detect abnormalities before the development of clinical symptoms and earlier than lung function indexes.[33]

Small airways are usually visible at the site of inflammation, accompanied by exudation. SAD can be seen indirectly through air retention when there is no obvious emphysema or bronchiectasis.[34] Due to distal hypoventilation, air retention, and low blood flow, a fixed obstruction of a small airway leads to patchy differences in density.[35,36] During a normal expiratory period, the cross-sectional area of the lung decreases with increased lung attenuation value; here, trapped air is defined as the loss of the reduced cross-sectional area of the lung and increased lung attenuation value.

Based on available data, we summarized the possible CT phenotypes as functional resolution, trapped gas, parametric response mapping, ventilatory function, and micro-CT. Table 1 lists the visually defined CT phenotypes observed during small airway obstructions in patient with COPD. Moreover, Table 2 summarizes the available researches on CT phenotypes in recent years.

Functional phenotypes of high-resolution computed tomography (HRCT)

HRCT is an ideal method for the detection and characterization of emphysema, as it offers a simple and easy way to quantify the degree of emphysema. Chest HRCT not only has a good correlation with lung function but also reflects the condition of small airway lesions.[37,38] A previous study compared 78 cases of patients with COPD at different stages of SAD. Evidently, both stenosis and occlusion in small airways appeared earlier than emphysema, indicating that CT examinations are superior in early diagnoses than detecting abnormalities of clinical symptoms and lung function index.[21]

Changes in small airways (both terminal and respiratory bronchi) are considered major early-stage COPD symptoms. However, for several reasons, CT is more difficult to use for small airway measurement than emphysema. CT imaging currently lacks the resolution to evaluate the thickness of small airway walls; thus, CT imaging studies mainly focus on larger airways and measure the thickness of the subsegmental bronchial wall in patients with COPD. It is difficult to apply CT in the routine evaluation of COPD in clinical practice due to the radiation exposure associated with CT.[39]

Studies have shown that patients with COPD who have mild emphysema and thickened bronchial walls, similar to asthmatic bronchitis and bronchial asthma, have more symptoms of wheezing.[40] Furthermore, the thickening of bronchial walls and airway stenosis incorporate more obvious airway inflammation, including more symptoms of cough and phlegm, which can be detected with CT. As for bronchial wall thickening, significant changes in

Table 2: Summary of researches on CT phenotypes of COPD in recent years.

Publication year	First author	Journal	Method	Main CT findings	No. of patients	Screened population	Target
2019	Charbonnier *et al*	Respir Med	Thin section thoracic CT	Pi10 is a clinically relevant biomarker of smoking-related airway injury in smokers with and without COPD	2046	Smokers with and without COPD	Airway wall thickening and smoking status
2020	Pompe *et al*	Radiology	Inspiratory and expiratory volumetric thoracic CT	FEV_1 accounted for less than 10% of emphysema progression and less than 50% of air trapping progression detected at CT	4211	Smokers with and without COPD	Emphysema and air trapping
2020	Liu *et al*	Chin Med J	Thoracic CT	Airway IgA concentrations in mild and moderate COPD patients are directly associated with the severity of COPD with "emphysema phenotype" preceding severe airway limitation	30	COPD with "emphysema phenotype"	Small airway and emphysema
2016	Subramanian *et al*	Eur Respir J	QCT	The group with mixed pathology had upper lobe predominant emphysema. Patients with mild disease had better spirometric measures than the other phenotypes	441	COPD subjects (GOLD 0–3)	Emphysema and airway disease
2020	Oh *et al*	Radiology	Inspiratory and expiratory CT	Participants with visual emphysema demonstrated progressive airflow obstruction with lower values of FEV_1/FVC and greater progression in quantitative emphysema measured by 15th percentile lung density	4095	GOLD 0 and participants with visually evident emphysema	Visually evident emphysema
2016	Hartley *et al*	J Allergy Clin Immunol	QCT	Air trapping measured based on expiratory/inspiratory ratio of mean lung density was significantly increased in patients with COPD and asthmatic patients	301	Smokers with COPD and asthma patients	Air trapping and emphysema
2019	Arjomandi *et al*	Eur Respir J	QCT	Subjects in higher RV_{CT}/TLC_{CT} tertile were more likely to develop spirometric COPD than those in lower RV_{CT}/TLC_{CT} tertile	849	Smokers without a clinical diagnosis of obstructive lung disease	Air trapping, emphysema and airway disease
2018	Occhipinti *et al*	Radiology	Inspiratory and expiratory CT	Gas trapping obtained by difference of inspiratory and expiratory CT density thresholds was highly correlated with that obtained by coregistration analysis	224	COPD patients (GOLD 1–4)	Emphysematous gas trapping
2018	Kirby *et al*	Am J Respir Crit Care Med	Inspiratory and expiratory CT	CT total-airway-count was significantly reduced by 19% in both GOLD 1 and GOLD 2 compared with never smokers and by 17% in both GOLD 1 and GOLD 2 compared to at-risk participants after adjusting for LAA950	1184	Never-smokers, smokers with normal spirometry at risk for COPD and GOLD 1–2	Total number of airways quantified in *vivo*
2016	Bhatt *et al*	Am J Respir Crit Care Med	PRM	Among GOLD 1–4 participants, for every additional 5% of lung affected by PRM_{fSAD} or PRM_{emph}, a significant decline in FEV_1 was seen	1508	COPD subjects (GOLD 0–4)	Emphysema and functional small airways disease
2018	Pompe *et al*	Respir Med	PRM and low dose CT	PRM_{emph} and PRM_{fSAD} were both higher in COPD participants as compared to non-COPD	195	COPD patients (GOLD 0–4)	Emphysema and functional small airways disease

(*continued*)

Table 2
(continued).

Publication year	First author	Journal	Method	Main CT findings	No. of patients	Screened population	Target
				participants and were higher with increasing GOLD stage			
2019	Vasilescu *et al*	Am J Respir Crit Care Med	PRM and micro-CT	TB numbers were reduced; surviving TB had increased wall area, decreased circularity, reduced cross-sectional luminal area, and greater airway obstruction	55	End-stage COPD treated by lung transplantation	Terminal bronchioles
2018	Tanabe *et al*	Eur Respir J	MDCT and micro-CT	On micro-CT, there was a reduction in the number of terminal bronchioles as well as a decrease in the luminal areas, wall volumes and alveolar attachments to the walls of TB bronchioles	15	Patients with very severe COPD waiting for lung transplantation	Small airway
2017	Tanabe *et al*	Am J Respir Crit Care Med	MDCT and micro-CT	The preterminal bronchiolar length, wall volume, total volume (wall+lumen), lumen circularity and number of alveolar attachments were reduced in both centrilobular and panlobular emphysema compared to controls	20	Patients with COPD waiting for lung transplantation	Preterminal bronchioles in emphysema
2018	Koo *et al*	Lancet Respir Med	Multiresolution CT and micro-CT	The number of terminal bronchioles decreased by 40% in patients with GOLD 1 and 43% in patients with GOLD 2, the number of transitional bronchioles decreased by 56% in patients with GOLD 1 and 59% in patients with GOLD 2	34	COPD patients (GOLD 0–4) and patients who had undergone lung transplantation	Terminal and transitional bronchioles
2016	Iyer *et al*	Am J Respir Crit Care Med	DECT	After sildenafil administration, regional PBV-CV decreased in susceptible smokers, but did not decrease in nonsusceptible smokers, after adjusting for age and pack-years	17	PFT-normal current smokers	Centriacinar emphysema
2016	Lee *et al*	Eur Radiol	DECT	The xenon ventilation change correlates with the parenchymal attenuation change	52	COPD patients	Parenchymal attenuation
2020	Humphries *et al*	Radiology	Thoracic CT	Deep learning emphysema classifications were associated with impaired pulmonary function tests, 6-min walk distance, and St George's Respiratory Questionnaire score at univariate analysis	7143	COPDGene participants	Emphysema pattern

COPD: Chronic obstructive pulmonary disease; COPDGene: Genetic Epidemiology of COPD; CT: Computed tomography; DECT: Dual-energy computed tomography; FEV_1: Forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IgA: Immunoglobulin A; Pi10: Hypothetical airway with internal perimeter of 10 mm; FVC: Forced vital capacity; LAA950: Low-attenuation area below −950 Hounsfield units; MDCT: Multidetector row computed tomography; PBV-CV: Perfused blood volume-coefficients of variation; PRM: Parametric response mapping; PRM_{emph}: Emphysema on parametric response mapping; PRM_{fSAD}: Functional small airways disease on parametric response mapping; micro-CT: Micro-computed tomography; PFT: Pulmonary function test; QCT: Quantitative computed tomography; RV_{CT}: CT-measured residual volume; TB: Terminal bronchioles; TLC_{CT}: CT-measured total lung capacity.

emphysema can be used to estimate the mortality risk on a patient by patient basis.[41] Moreover, end-expiratory CT scans are a good way to assess gas retention in patients with COPD; most studies assess the presence of gas retention by low attenuation percentage at a threshold of either -856 or -850 Hounsfield units (HU) (low attenuation areas [LAA]-856 HU or LAA-850 HU).[42,43] Significantly, Murphy *et al*[44] found a correlation between LAA-850 HU and FEV_1/forced vital capacity (FVC) and the ratio of FEV_1 to predicted value ($r = 0.85$–0.90) in 216 smokers.

Overall, the above research demonstrated the use of HRCT as an important potential tool in the evaluation of COPD.

In particular, HRCT may be a substitute for spirometry in certain situations.

Trapped gas CT phenotype

Accumulating evidence suggests that small airway disease is a key pathological feature of COPD. It is generally believed that air trapping is associated with small airway lesions, and that it is an important phenotype of COPD. Multiple studies have shown that lung function impairment is causatively related to trapped air and proximal airway stenosis in patients with asthma and COPD.[45]

Trapped air is an indirect HRCT measurement for small airway dysfunction. The lung lobules are overinflated due to airway obstruction.[46] Moreover, trapped air is linked to lung function decline in patients with COPD. However, this phenomenon was also observed in healthy non-smoking subjects without airflow blockages. In patients with COPD, the imaging findings are further complicated in the presence of emphysema. At least in clinical settings, air trapping remains a qualitative marker for SAD and may be beneficial for the diagnosis and monitoring of COPD. When all CT indices, including those of air trapping, emphysema, and airway disease, were included in the same model, only radiographically-measured residual volume (RV) to total lung capacity (TLC) ratio (RV_{CT}/TLC_{CT}) retained their clinical significance. Increased trapped air predicts the decline of lung function and the progression of COPD in smokers without airflow limitation.[47]

Although several studies have quantified gas retention in COPD, further investigations are required to determine the best approach. For example, the relative contribution of gas trapping, obtained by co-registration of inspiratory and expiratory CT scanning, can be determined by differences calculated using inspiratory and expiratory density thresholds. Intriguingly, CT scanning predicts the extent of emphysema in parallel with both the PFT and body mass index.[48]

Parametric response mapping phenotype

CT images have recently been used to obtain the inspiratory and expiratory phases to evaluate functional SAD (fSAD), which is caused by an emphysema-related low attenuation area and trapped air. The parametric response map (PRM) detection method was formed via processing of the inspiratory and expiratory phases of CT images.[49,50]

As a CT-based method to define phenotype of patients with COPD, PRM is capable of differentiating emphysema from non-emphysema-related trapped air, which aids in identifying the overall extent and localization of the disease. Given the relative contributions of fSAD and emphysema in COPD phenotypes, PRM serves as a complementary readout to PFTs and CT-based metrics, thereby aiding in the personalized diagnosis and management of COPD.[51]

PRM_{fSAD} identifies areas of loss, narrowing, and obstruction of terminal bronchioles, thereby providing a non-invasive imaging methodology to identify small airway damage in COPD.[52] Recently, PRM has been applied to assess lung function decline after lung transplantation as well as diagnose complications related to hematopoietic stem cell transplantation.[53,54] Moreover, multiple genes were found to be associated with PRM_{Emph}, indicating the essential role of PRM in recognizing the development of emphysema.[55]

Ventilatory function CT phenotype

Dual-energy CT lung ventilation imaging, based on xenon enhancement, can provide both anatomical information and ventilation function information for both the whole and local lung.[56] Xenon-enhanced dual-energy CT is now used extensively for clinical evaluations of lung function.[57] The exhaled xenon flow out (wash out) was negatively correlated with lung function, especially in the emphysema region, where there was a significant dynamic change in inhaled and exhaled xenon ventilation.

Regarding CT images, different ventilation modes are associated with different compositions of COPD on CT images, which is helpful in determining the etiology of COPD based on airflow limitation severity.[58] In fact, an alternative test has recently emerged, allowing multiple lung volumes to be scanned without contrast. For example, combined with advanced image processing techniques, the standardization of CT scans on total lung volume and residual air volume results in a good pulmonary ventilation function map and relevant assessment.

Micro-CT phenotype

The micro-CT allows extremely high resolution (1 μm/voxel), shows stunning images of the alveoli and terminal airways, and even realizes "virtual bronchoscopy" through alveolar ducts; it is an ideal method for dissecting the lung tissue, including small airways.[59] A combination of multidetector row CT, micro-CT, and histology provides more information on the pathological changes in small airway obstructions.[60,61]

In COPD, micro-CT can demonstrate loss of terminal bronchioles at early stages of the disease before microscopic emphysema. Moreover, it is possible for micro-CT to anatomically identify the terminal bronchioles, count the number of typical lung tissue samples, and subsequently calculate the total number of terminal bronchioles. Additionally, direct measurements, indicating the total number of bronchioles, as well as the average lumen cross-sectional area, provide a total cross-sectional area of terminal bronchioles in the lung.[62] Consistent with previous literature, time-dependent dynamic changes in micro-CT have been illustrated in a murine model of chronic cigarette smoke exposure.[63]

The combination of micro-CT and histology showed a decrease in the total number of terminal bronchioles, with thickening of bronchiolar walls in survivors. Some scholars have elegantly combined micro-CT with PRM in COPD research. Hoff *et al*[64] found that the surface area of fSAD (S^{fSAD}) was the most robust and significant independent indicator of COPD in the clinic. Using micro-CT of human lung specimens, they also confirmed structural differences

associated with unique S^{fSAD} patterns; furthermore, they demonstrated that longitudinal feature alterations occurred with worsening pulmonary function, independently of an increase in disease extent.

Importantly, only small samples from lung tissue or experimental animals can be imaged by micro-CT. In addition, these samples are exposed to high doses of radiation, which are harmful to living tissues.[65] Although micro-CT is confined to research for the moment, this technology may play a role in the future.

Clinical Application of CT in Small Airway Detection

CT examinations often describe the anatomical structure in detail, with a minimum of 200 to 300 μm resolution, equivalent to the seventh to ninth grade bronchus of the lung.[66] Bronchioles can be automatically identified by HRCT through processing of the data. Furthermore, CT phenotypes have also been used to guide clinical treatment. For example, patients with COPD with the mixed phenotype are associated with more severe dyspnea and frequent hospitalizations than those with each of the remaining CT-based phenotypes. Thus, more attention and appropriate interventions should be paid to patients with mixed COPD phenotypes.[67] By using a novel multiresolution CT imaging protocol, a cross-sectional analysis showed that the development of airflow limitation in COPD involves progressive destruction and loss of the terminal and transitional bronchioles before a decline in lung function is observed.[68] This suggests that early intervention for disease modification in mild or moderate COPD cases is essential.

CT detection can also reflect the severity of COPD, as changes have a greater impact on airflow limitations in small- and medium-sized airways. The presence and severity of emphysema in patients with COPD can be estimated by the mathematical modeling of the airway function derived from standard spirometry and quantified by CT metrics and radiomics.[69] Quantitative CT (QCT) can detect short-time progression of emphysema in severe COPD.[70] The changes partly differed among lung lobes and airway generations, indicating QCT as a useful method to address the heterogeneity of COPD.

Additionally, CT scans can predict the progression of COPD and exacerbations. Among participants with airflow obstruction, every 5% increase in CT emphysema was independently associated with a 3.5 mL additional decline in FEV_1 in mild-to-moderate stage COPD each year.[25] The rate of FEV_1 decline is the greatest in functional SAD. Acute exacerbation of COPD is an acute event characterized by the worsening of respiratory symptoms. Patients with both emphysema and airway wall thickening are more symptomatic, have poorer pulmonary function, and have more frequent severe exacerbations.[71] These facts suggest that CT phenotypes may have important clinical applications.

CT examination of the small airway wall changes in COPD

Small airway walls in the lungs are usually less than 1 mm thick. In COPD patients, the infiltration of inflammatory cells results in increased airway wall thickness as well as changes in the density of small airways.[72] Upon CT scanning, the average attenuation value of the lung is lower than that of the small airways, and the peak attenuation value can be obtained via reconstruction algorithm involving airway wall thickness and density.

Washko *et al*[73] conducted a computer-based simulation study, showing that the attenuation value of airway walls can measure the changes in airway wall thickness and density. These findings are applicable to assess the thickness of airway walls in patients with COPD. The peak attenuation value has the highest correlation with the percentage of total airway area.[74]

Accurate assessment of small airways on thoracic quantitative CT scans in COPD

As the main site of airflow obstruction in COPD, the small airway cannot be directly displayed by CT. Actually, it can be obtained by quantitative analysis of gas density during exhalation. An increase in the total amount of residual gas reduces lung density at the end of the expiratory period, owing to the combined effect of decreased elastic pulmonary function caused by emphysema and increased airway resistance.[75] The variation amplitude of low attenuation value between inspiratory and expiratory scanning reflects the degree of trapped air and other pathological characteristics of small airways, as assessed by professional software.[76,77] Remarkably, emphysema occurs in patients with COPD and emphysema itself contains residual gas; thus, it is a confounding factor for the measurement of small airways.[78]

When the density threshold is fixed at −856 HU, the main limitation is the inability to distinguish low density areas that are associated with small airway destruction-related emphysema.[79] Although the air is retained in the lungs, the low-density area still looks normal on scanning, even if the small airway has been destroyed. Therefore, many researchers have focused on this method of small airway measurement. An attenuation value between −860 and −950 HU in inspiratory and expiratory CT scans suggests a relative volume change closely related to the prediction of FEV_1/FVC and FEV_1%. This indirect quantification of the airway has three advantages. Firstly, there is no need to consider the airway classification and the airflow limitation. Secondly, the CT attenuation value has greater correlation with pulmonary function than the bronchial size. Finally, it can provide regional assessment. However, there is still some overlap between the trapped air caused by SAD and trapped air caused by emphysema, and this interference cannot be eliminated.

The reliable and repeatable CT scans are difficult to obtain in patients with severe COPD. So, it is difficult to measure lung volume and the trapped air value. Undoubtedly, the correlation between continuous examinations may be limited. Multiple aspects are needed to calculate relative lung area or lung volume. Meanwhile, the results may be unreliable due to errors in post-processing.[80] Hersh *et al*[81] suggested that quantitative measurement based on

paired inspiratory and expiratory chest CT scans can be used to assess small airway disease in smokers with and without COPD and to predict the prognosis of patients. For paired inspiratory and expiratory CT scans to quantify small airway obstruction, data collection should be pre-calibrated to help overcome possible errors.[82]

Factors affecting quantitative measurement

Although chest CT is beneficial in depicting regional lung function, air content in the lung, and emphysema (<−950 HU), imaging the small airways remains a challenge. Some of these limitations are as follows: static images cannot provide the required insight on lung function and dysfunction, limited resolution of clinical CT scans on lung architecture, and challenges that the biomedical community faces when trying to translate discovery into therapy. Such limitations may be addressed through novel image analysis techniques, upcoming CT-based and magnetic resonance imaging (MRI)-based technologies, closer ties between academia and industry, and an expanded endeavor to share data across the biomedical community.

The quantitative value of trapped air in expiratory scanning is notably affected by the expiratory level. However, the effect of expiration on trapped air has not been well elucidated. The scan should be followed by a strict breathing order, which can also be standardized by using a hilar lung scan that is technically cumbersome and not widely used in clinical practice. However, it is unknown whether this standardization will improve the repeatability of quantitative evaluation of air retention.[83]

Besides, the noise of low dose scans may affect quantitative measurements of trapped air, similar to that in the quantification of emphysema.[84] At present, there is no noise reduction filter to verify the effect of increasing image noise removal on the quantification of air capture; moreover, there is no research involving the quantitative measurement of sectional thickness of air retention using CT and other scanning parameters.[85] Furthermore, the presence of emphysema may affect the quantitative assessment of trapped air.

Artificial intelligence (AI) and deep learning

AI has become a hot topic in radiology. Thoracic imaging is an important domain for developing solutions based on AI.[86] Deep neural networks are one of the main techniques behind the explosion of AI as a powerful tool to improve the outcome prediction. Specifically, convolutional neural network analysis can identify smokers who have COPD and predict who are most likely to have acute respiratory disease events and those with the highest mortality risk.[87] Humphries *et al*[88] described that deep learning emphysema classifications were associated with impaired PFTs, 6-min walking distance, and St. George's Respiratory Questionnaire. Also, deep learning can help identify individuals at greater risk of mortality and may be a more sensitive indicator of the risk. Deep learning can be used to reliably automate quantification of air trapping and emphysema from inspiratory and expiratory CT. It facilitates staging of COPD severity, has a diagnostic performance comparable with that of spirometric GOLD staging, and provides further prognostic value when used in conjunction with GOLD staging.[89]

Conclusions and prospects

PFTs are regarded as the gold standard for the diagnosis of COPD. Although small airway changes occur at early stages of COPD, lung function often remains in the normal range. Small conducting airways were found to be a silent zone where disease could accumulate over time in combination with epidemiological evidence for a susceptible minority; this, alongside the understanding that cigarette smoking accelerates the age-related decline in FEV_1, led to the search for specialized physiological tests to detect disease abnormalities earlier, in order to prevent disease progression.

Patients should be screened at early stages for the diagnosis, treatment, and prevention of COPD. The small airway CT phenotype, compared with the pulmonary function index, can accurately reflect the disease severity in patients with COPD, which is conducive to improving the prognosis of this disease. However, the current available CT technology cannot directly display small airways. Therefore, air retention quantification is assessed by end-expiratory CT scans that can be used as an indirect measurement for SAD. Further investigations on functional CT phenotypes in small airway obstructions are warranted to shed new insights into the diagnosis and treatment of COPD.

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Conflicts of interest

None.

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