

Evaluation of small airway function and its application in patients with chronic obstructive pulmonary disease (Review)

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Abstract. Chronic obstructive pulmonary disease (COPD) is a chronic airway inflammatory disease characterized by incomplete reversible airflow limitation. The diagnosis of COPD is mainly based on pulmonary function examination. In recent years, it has been indicated that small airway dysfunction occurs in patients with all stages of COPD, even in high-risk smoking groups who have not yet met the diagnostic criteria for COPD. Early recognition of small airway dysfunction and early initiation of small airway targeted therapy have become foci of research. In the present review, the methods of evaluating small airway function were summarized and their merits and shortcomings were discussed. Furthermore, the potential of targeted treatment of small airways in patients with COPD was outlined.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a type of chronic airway inflammatory disease. The clinical symptoms of COPD are chronic cough, expectoration of sputum, wheezing and shortness of breath. COPD is typically marked

by high rates of morbidity and mortality, and the lack of early diagnosis imposes a heavy economic and social burden on the world (1). In recent years, it has been indicated that small airway dysfunction occurs in patients with all stages of COPD, even in high-risk smoking groups who have not yet met the diagnostic criteria for COPD (2). There is increasing interest to detect small airway dysfunction and screen patients suspected to have COPD early. There are numerous methods for detecting small airway dysfunction but there is no consensus on the gold standard for diagnosis (Table I). Furthermore, small airway targeted therapy is still in the exploratory stage. Therefore, the aim of the present review was to elaborate on the assessment of small airway function and targeted treatment of small airways in patients with COPD.

The small airways, which are the peripheral airways, whose internal diameter is <2 mm, are located from the seventh or eighth generation of airways to the respiratory bronchioles. As a consequence of their small lumen diameter, the wall is mostly without cartilage, the total cross-sectional area is large and airflow velocity is slow; thus, small airways are relatively more vulnerable to damage by toxic particles and harmful gases, thus leading to stenosis and occlusion (3). In recent years, as research has progressed, it has been indicated that small airway diseases are widely present in various diseases, particularly COPD. In patients with COPD, peripheral airways, rather than proximal airways, are the predominant site of airflow resistance (4). The small airways of patients with COPD have various lesions due to processes including airway remodelling, mucous plugging and neutrophil and lymphocyte infiltration, and ultimately, the volume of small airways decreases. Furthermore, the degree of inflammation, airway wall thickness and the number of small airways are all correlated with the severity of the disease (5). In addition, small airway dysfunction is closely related to certain patient clusters of COPD who are exposed to smoke and biomass and who have more severe clinical manifestations and frequent exacerbators (6). Therefore, early recognition of small airway dysfunction and early initiation of small airway targeted therapy are of great significance.

2. Evaluation of small airway function

Spirometry. Spirometry is the most commonly used method in the assessment of pulmonary ventilation. The indicators of

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forced expiratory flow (FEF)50%, FEF75% and FEF25-75% [also known as maximum midexpiratory flow (MMEF)], are the most frequently used to evaluate the function of small airways. It is now generally accepted that there is small airway dysfunction when two of the above three indicators are below the expected value of 65% (7). It has been indicated that MMEF may be used to screen patients with suspected early COPD who have clinical symptoms, but whose pulmonary function examination has not yet detected the presence of persistent airflow limitation, suggesting that MMEF may be used as an indicator of small airway dysfunction in early COPD (8). These indicators are easy to obtain, but MMEF relies on forced vital capacity (FVC) measurement, with poor reproducibility and sensitivity. Furthermore, there is a small correlation between MMEF and other indicators, such as gas trapping and small airway inflammation determined by lung biopsies obtained through bronchoscopy. Therefore, the American Thoracic Society does not support its use for determining small airway disease (7). In addition, compared with MMEF, there are numerous other indicators of small airway function with better accuracy and sensitivity. Forced expiratory volume (FEV) in 3 sec (FEV3)/FVC and the fraction of air not expired in the first 3 sec (1-FEV3/FVC) are significantly correlated with gas trapping and lung hyperinflation (9). In addition, FEV1/FEV6 and FEV3/FEV6 are more sensitive than FEV1/FVC in the detection of early airflow limitation (10). Furthermore, the ratio of FVC to slow vital capacity may be an alternative marker for small airway collapse (11).

Plethysmography. Plethysmography is a method of lung volume examination that cannot be directly measured by spirometry. Residual air volume (RV) and RV/total lung volume (TLC) are commonly used to assess small airway function and provide accurate information about gas trapping and lung hyperinflation. It is now generally accepted that there is small airway dysfunction when RV is >120% of the predicted value or RV/TLC is >35% (12). Furthermore, studies have indicated that RV and RV/TLC are closely related to the degree of airway inflammation in small airways (13). The method has the advantages of a simple operation, better accuracy and precision, and high reproducibility; on the other hand, it is not specific to small airways and the equipment is expensive and occupies a large area, so it is currently not widely used.

Impulse oscillometry (IOS). IOS, based on the forced oscillation technique, is a simple and noninvasive novel method of lung function assessment. It has been indicated that it may be used to assess small airways. IOS parameters, such as total airway resistance (R5)-central airway resistance (R20), peripheral capacitance, resonant frequency (Fres) and reactance area (AX), are significantly correlated with FEF25-75%, particularly Fres, which is more sensitive than FEF25-75% in the diagnosis of small airway dysfunction (14). In patients with COPD and heavy smokers, Fres and R5-R20 are significantly correlated with the small airway area measured by intrabronchial optical coherence tomography (15). In addition, IOS may also be used to evaluate the severity of COPD, distinguish the site of obstruction, discriminate asthma from COPD and evaluate treatment effects (16). The novel approach has a number of advantages over other methods. One of the

biggest advantages is that it is effort-independent (portable, user-operated capnograph devices and related methods), so it is thought to be of great potential.

Gas washout techniques. Gas washout techniques have been used in clinical practice for numerous years. Nitrogen is the most commonly used gas and in recent years, there has been increasing interest in helium washout systems.

Single breath nitrogen washout (SBNW). SBNW uses the principle of conservation of energy. During the process, patients inhale 100% oxygen and then the nitrogen contained in the alveoli is gradually flushed and diluted, thus producing a curve representing the nitrogen concentration. According to the concentration of nitrogen in the exhaled air, the distribution of air in the lung is analysed. This may reflect the small airway functions of the closed volume (CV), closing capacity (CC) and third phase slope III (SIII). CV refers to the amount of remaining gas at the beginning of small airway closure. In healthy individuals, small airway closure occurs near the RV. CC refers to the total amount of CV and RV. A study indicated that the increase in CV and CC in patients with COPD was related to gas trapping caused by the premature closure of small airways. SIII refers to the slope of the third stage of the curve, which is normally a smooth curve with a slight upward trend and provides information on the ventilation distribution inhomogeneity (17). In patients with COPD, SIII exhibits obvious increases, which is related to lung ventilation inhomogeneity; furthermore, SIII is correlated with FEV1%, RV/TLC and diffusion capacity to carbon monoxide (DLCO) (18).

Multiple breath nitrogen washout (MBNW). MBNW represents an improvement over the SBNW test. The patient inhales 100% oxygen through a series of tidal breathing and then nitrogen is gradually washed out until the exhaled nitrogen concentration is nearly 1/40 of the initial concentration. A measure frequently used to assess the overall gas mixing efficiency of the lungs is the lung clearance index (LCI). If ventilation distribution inhomogeneity increases, nitrogen removal is delayed and the LCI increases. A study has indicated that LCI may be used to evaluate early airway function in patients whose COPD diagnosis has not yet been confirmed with spirometry (19). Scond and sacin reflect the ventilation heterogeneity of the conducting airway and small airway in the acinar area, respectively. In smokers who have not yet met the diagnostic criteria for COPD, scond and sacin are able to detect small airway dysfunction prior to spirometer examination, particularly sacin (20). Furthermore, they may also be used to evaluate the severity of COPD (21). In addition, according to research, smokers with reduced pulmonary DLCO are more likely to develop COPD. Furthermore, in patients with mild to moderate COPD, DLCO is associated with small airway disease parameters, such as parametric response mapping (PRM) defined by CT scan, suggesting that the decrease in DLCO may indicate small airway dysfunction (22). The MBNW test requires a low level of patient cooperation, but it has not been widely used in clinical practice due to the requirement for standardized techniques.

Helium washout test. As a tracer gas, helium is less dense and is able to penetrate deep into the lungs for a certain period

Table I. Advantages and disadvantages of methods for the assessment of small airway function.

Method	Parameters	Advantages	Disadvantages
Spirometry	FEF50, FEF75%, MMEF, FEV3/FVC, 1-FEV3/FVC, FEV1/FEV6, FEV3/FEV6, FVC/SVC	Noninvasive, easy to perform, highly sensitive, promising	Poor reproducibility and sensitivity, not correlated with inflammation, only reflects the overall function of the lungs, further studies needed
Plethysmography	RV, RV/TLC	Accuracy and reproducibility, correlates well with inflammation	Occupying large area, costly, not widely available
Impulse oscillometry	X5, AX, Fres, R5-R20	Noninvasive, easy to perform, highly sensitive, effort-independent ^a	Not widely available, further studies needed
Single breath nitrogen washout	CV, CC, SIII	Sensitive to early change, good reproducibility and sensitivity	Difficult to perform, not widely available
Multiple breath nitrogen washout	LCI, Scond, Sacin, DLCO	Good reproducibility and sensitivity, effort-independent	Difficult to perform, not widely available
Helium washout test	-	Highly sensitive, good repeatability and reliability	Further studies needed
Exhaled nitric oxide	FeNO, CANO	Noninvasive, easy to perform	Further studies needed
High-resolution computed tomography	MLDE/I, PRM, DPM	Direct imaging of the lungs, easy to perform	Costly, exposure to radiation
Hyperpolarized magnetic resonance imaging	VDS, ADC	Highly sensitive, no risk of radiation exposure	Costly, technically demanding
Intrabronchial optical coherence tomography	-	Direct assessment of the airway structure	Further studies required
Serum markers	Examples: Club cell 16 protein, CXCL8, CX3CL1, PAI-1	Easy to obtain	Further studies required
Induced sputum	Example: Pentosidine	Noninvasive	Further studies required
Bronchoalveolar lavage	Example: MMPs	-	Invasive, further studies required
Bronchoscopy biopsy	-	-	Invasive, rarely used in everyday practice

^aPortable, user-operated capnograph devices and related methods. FEF, forced expiratory flow; MMEF, maximum midexpiratory flow; FEV, forced expiratory volume; FVC, forced vital capacity; SVC, slow vital capacity; RV, residual air volume; TLC, total lung volume; X5, peripheral capacitance; AX, reactance area; Fres, resonant frequency; R5, total airway resistance; R20, central airway resistance; CV, closed volume; CC, closing capacity; SIII, third phase slope III; LCI, lung clearance index; DLCO, diffusion capacity to carbon monoxide; FeNO, fractional exhaled nitric oxide; CANO, alveolar concentration of exhaled nitric oxide; MLDE/I, mean lung density between expiratory and inspiratory; PRM, parametric response mapping; DPM, disease probability measure; VDS, ventilation defect score; ADC, apparent diffusion coefficient; CXCL8, C-X-C motif ligand 8; CX3CL1, CX3C chemokine ligand 1; PAI-1, plasminogen activator inhibitor-1; MMPs, matrix metalloproteinases.

of time, so it may also be used for gas washout techniques. According to research results, compared with the nitrogen washout test, the helium washout test is more sensitive to ventilation distribution inhomogeneity in the small airway (23). In addition, the sulfur hexafluoride and helium double-tracer gas washout test are able to detect early inflammatory changes in the small airways, similar to the nitrogen washout test, with better repeatability and reliability (24).

Exhaled nitric oxide (NO). NO, which is produced by airway cells and lung inflammatory cells, is able to reflect the level of inflammation in the lung, particularly eosinophilic airway

inflammation. The measurement of the exhaled NO is flow rate-dependent. At low speed, NO mostly reflects the fractional exhaled NO (FENO) which comes from the central airway, whereas at high speed, it reflects the alveolar concentration of exhaled NO (CANO) which arises from the peripheral airway. FENO has been widely used in the clinical evaluation of central airway inflammation and therapeutic effects, although CANO is still under examination. According to certain studies, CANO increases in patients with COPD and increased CANO is related to changes in VC, RV/TLC, SIII and DLCO. After treatment, patients exhibited improvement in CANO and improved CANO correlated with other improved small airway

indicators, suggesting that the CANO level is able to reflect peripheral airway dysfunction and may help predict clinical response to inhaled corticosteroids (25,26). CANO measurement does not require any sophisticated equipment, but it is derived from computational extrapolation, rather than being directly quantified. Further research is required to determine its value.

Imaging technology. High-resolution computed tomography (HRCT) is a noninvasive method that provides anatomical details of the bronchial tree. The resolution threshold of HRCT is 1 mm, whereas the thickness of the distal airway wall is 0.6-1 mm. Therefore, it is still difficult to directly evaluate distal small airways. Currently, local gas trapping manifests as a mosaic attenuation area in HRCT caused by small airway lesions and is frequently used to indirectly evaluate small airways in clinical practice. However, the above performance is not specific and mainly depends on visual assessment and strong subjectivity. The ratio of mean lung density between expiratory and inspiratory CT (MLDE/I) is able to quantitatively evaluate the degree of gas trapping (27). However, as both emphysema and small airway disease in patients with COPD lead to areas of low attenuation and may independently predict the severity of COPD and airflow obstruction (28), it is important to identify whether gas retention is due to small airway disease or emphysema. It has been indicated that PRM and disease probability measure are able to identify the degree of functional small airway disease and emphysema and correlate well with FEV1, FEV1/FVC, RV/TLC and dyspnoea symptoms, suggesting that they may be used as novel indicators to identify small airway dysfunction (29). In recent years, investigators have focused efforts on improving the resolution of CT, and ultra-HRCT techniques have also developed rapidly and are able to accurately and directly evaluate peripheral airways with a diameter of 1-2 mm (30). Although CT is a useful, noninvasive tool for indirectly assessing small airway function, its use has been limited due to exposure of patients to radiation.

Conventional magnetic resonance imaging is rarely used for lung imaging due to technical limitations. Hyperpolarized magnetic resonance imaging is an increasing area of interest. Patients are required to inhale a polarized gas, such as helium, into the lungs, where it diffuses freely until it is blocked by the airway and alveolar walls. The signal distribution of hyperpolarized gas may provide ventilation images of pulmonary structures, reflecting local airflow and ventilation heterogeneity. ^3He is the most commonly used hyperpolarized gas. The ventilation defect percent and apparent diffusion coefficient (ADC) are commonly used in the assessment of small airway function. The ventilation deficiency score identifies small airway impairment in early smokers with normal lung function (31). With ^3He magnetic resonance imaging of healthy controls and patients with COPD, inhalation of hyperpolarized gas distributes reasonably homogeneously in healthy young adults, whereas patients with COPD have uneven signal distribution with patchy or wedge-shaped defects. Ventilation defect scale and pulmonary function test and emphysema detected by HRCT have a good correlation (32). Another commonly used index is the ADC, i.e., the diffusion motion of the hyperpolarized gas. Significant

differences in ADC values between patients with COPD and healthy controls were detected and there were significant correlations with FEV1, RV, TLC, DLCO and PRM measured by CT (33). Indeed, ADC was more sensitive than MLDE/I in distinguishing patients with COPD from healthy controls and was more strongly correlated with DLCO (34). Further study also suggested that multiparametric response maps based on CT and ^3He MRI are able to detect emphysema and small airway dysfunction in former smokers with normal pulmonary function and CT manifestations (35). However, ^3He is a rare isotope whose source is limited to a certain extent. Investigators then focused their efforts on ^{129}Xe MRI. ^{129}Xe is not only abundant in source but also, compared with ^3He MRI, ^{129}Xe MRI is able to identify ventilation defects and ADC abnormality more sensitively (36). In conclusion, hyperpolarized magnetic resonance imaging has no risk of radiation exposure. However, this method has a high cost and technical requirements and has only been performed in a small number of research centres.

In recent years, nuclear medicine technology has developed rapidly and it has been demonstrated that ventilation/perfusion single photon emission computed tomography using Technegas technology-marked $^{99\text{m}}\text{Tc}$ ultrafine carbon particles is able to detect early changes in small airways and grade the severity of small airway disease and lung function; furthermore, it is more sensitive than pulmonary and CT (37).

The diameter of traditional optical coherence tomography (OCT) exceeds the diameter of small airways and cannot be used to evaluate them. Endobronchial optical coherence tomography (EB-OCT) is a novel imaging method that is able to display the high-resolution cross-sectional structure of the airway wall. EB-OCT, which combines a superfine bronchoscope with novel navigation technology, is a new form of imaging. It is able to display the high-resolution cross-sectional structure of the airway wall and obtain more information on small airway walls, which is related to computed tomography and histological measurements (38).

Serum markers. In recent years, numerous serological indicators have been determined to reflect small airway obstruction, such as Club cell 16 protein, chemokines, particularly CXCL8 and CX3CL1 and plasminogen activator inhibitor-1. This method is more convenient, but further studies are needed (39-41).

Induced sputum. In recent years, certain studies have indicated that pentosidine in induced sputum exhibits obvious increases in COPD, which has a good correlation with mosaic attenuation of HRCT measurements and SIII, suggesting that it may be used as a potential biomarker of small airway obstruction (42).

Invasive operations. In addition, there are certain invasive methods, such as bronchoalveolar lavage and bronchoscopy biopsy, which may directly evaluate inflammation of the small airways. For instance, MMPs in bronchoalveolar lavage fluid may be used as a potential indicator of small airway function, particularly MMP8, which is significantly correlated with MLDE/I measured by CT (43). However, such methods are rarely used in routine clinical practice due to their invasive nature.

3. Treatment/management of COPD

To prevent COPD, smoking cessation, as well as masking of non-cigarette forms of smoke exposure coming from cigars and biomass fuel, should be adopted (44). Routine management of COPD, albuterol, tiotropium and beclomethasone dipropionate (BDP), as well as spacers and peak flow meters, should be provided. If necessary, a nebulizer and pulse oximeter should also be added for support. The inhaled route for drug delivery and long-acting bronchodilators are recommended. Combined medication of long-acting muscarinic antagonist (LAMA)/long-acting beta agonist (LABA) is able to better improve lung function (improved FEV1 and transition dyspnoea index) and clinical status (reduced probability of short-term COPD worsening) for patients with COPD compared to those treated with LAMA or LABA monotherapy in a clinical randomised trial, and safety profiles were similar between treatments (45). Accordingly, LAMA/LABA dual therapy has been outlined in the GOLD 2021 guidelines for COPD due to its efficacy and safety (44). If, with either a history of ≥ 2 moderate exacerbations or hospitalization(s) attributable to exacerbation, either serum eosinophilia (> 300 cells/ μ l) or coexisting with asthma is present, inhaled steroids are strongly recommended. In a randomized trial involving 10,355 patients with COPD, the rate of moderate or severe exacerbations in the triple-therapy group was lower than that in the dual therapy group (0.91 vs. 1.07, $P < 0.001$) and the annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was also lower than that in dual therapy group (0.13 vs. 0.19, $P < 0.001$) (46). Therefore, triple drug therapy (inhaled steroid/LAMA/LABA) has been recommended in the GOLD 2021 guidelines for COPD (44) and has become a standard scheme (47). In addition, hospitalized patients with COPD should supplement vitamin D if they are assessed for the severe vitamin D deficiency (< 10 ng/ml or < 25 nM) (48). In a randomised controlled trial, it was determined that vitamin D supplementation safely and substantially reduced the rate of moderate/severe COPD exacerbations in patients with baseline 25-hydroxyvitamin D levels < 25 nM but not in those with higher levels (49). Another randomized, double-blinded, placebo-controlled clinical trial suggested that consumption of 50,000 IU vitamin D3, as a convenient supplementation to a daily diet, was able to increase quality of life in patients with COPD (50).

Apart from medical management, interventional procedures such as endobronchial valves are recommended according to appropriate indications such as hyperinflation, dyspnoea and health status (51). In consideration of the COVID-19 pandemic, patients with COPD should be tested to exclude COVID-19 and should wear surgical masks, maintain physical distance to avoid face-to-face contact, and then continue their medications as mentioned above (44).

The current pharmacological treatment of COPD is based on an inhalation preparation, whose drug particles are large, so most of them are deposited in the oropharynx and the atmospheric tract; only a small percentage of them reach the distal airways. Therefore, certain researchers hold the opinion that the symptoms of numerous patients have not been improved by the use of regular medication in clinical practice, which may be related to poor targeting of the distal airways (8). To date,

the importance of targeted therapy for the small airways in clinical practice remains to be fully acknowledged and there is only a small number of studies specifically targeting the function and inflammation level of small airways in patients COPD prior to and after treatment, which leads to difficulties relating to how to achieve targeted therapy for small airways (52,53). The administration of theophylline to patients with COPD with irreversible air-flow obstruction improved the small airway function manifested as ameliorating air trapping and airway resistance (52). The extrafine combination of BDP and formoterol (BDP/F) and the extrafine combination of extrafine BDP/formoterol fumarate (FF)/glycopyrronium bromide (GB) provide the possibility of targeted treatment of small airways. Studies have indicated that, compared with traditional preparations, the extrafine combination of BDP/F is able to better improve the residual air volume and total lung volume and significantly improve dyspnoea symptoms (43). In addition, using functional respiratory imaging it was demonstrated that the extrafine combination of BDP/FF/GB has high lung deposition and peripheral airway deposition (54). In the future, the development of delivery devices and novel drug formulations aimed at small airway treatment are required.

4. Conclusion

Small airway diseases are widely present in COPD and have not received sufficient attention to date. Early recognition of small airway dysfunction and targeted treatment may improve clinical symptoms and delay disease progression. Whether there is a more convenient and accurate method to diagnose small airway dysfunction and how to better achieve targeted treatment of the small airway are questions to be addressed by future research.

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Availability of data and materials

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Authors' contributions

YL, XYL, HLW and LRY drafted the manuscript and table. MP edited, revised and approved the final version of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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