BMC Geriatrics

RESEARCH

Open Access

Effect of small airway dysfunction on large airway function parameters in elderly adults

Jing Pan[1], Yongke Zheng[1], Wen Lin[2] and Hui Chen[3*]

Abstract

Background To investigate the effect of simple small airway dysfunction (SAD) on large airway function parameters in old people.

Methods Elderly patients aged 60–80 years with complete pulmonary function data including the measured/predicted values of ≥ 80% for each of forced expiratory capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow (PEF), and FEV1/FVC ≥ 70% were included. Patients with no known smoking history, normal chest computerized tomography, and the measured/predicted values of ≥ 70% for each of maximal flows at 50% and 25% of remaining FVC (MEF50 and MEF25) and maximum mid-expiratory flow (MMEF) were categorized into the control group, whereas patients with the measured/predicted values of < 65% for more than 2 of MEF50, MEF25, and MMEF were divided into the observation group. 104 patients with simple SAD (observation group) and 102 patients with normal pulmonary function (control group) were selected.

Results The parameters of small airway function including MEF50, MEF25, and MMEF were positively correlated with slow vital capacity (SVC), FVC, FEV_1, PEF, and MEF75 in the large airway in both groups ($r = 0.280–0.634$). Except for PEF, the other 5 parameters in the observation group were significantly different from those in the control group. There was no significant difference between total lung capacity (TLC) and functional residual capacity (FRC), but there were significant differences between residual volume (RV), RV/TLC, diffusion capacity for carbon monoxide (DLCO), and specific diffusing capacity (KCO). There were 66 cases of SVC-FVC > 0 (FVC/SVC < 1) (66/104, 63.46%) in the observation group) and 45 cases of the control group (45/102, 44.12%), and the difference between the two groups was statistically significant. The area under the curve (AUC) of SVC-FVC and FVC/SVC in the prediction of SAD was 0.631 and 0.639, respectively, with a sensitivity and specificity of 63%.

Conclusions Simple SAD was associated with large airway pulmonary function, and PEF may not be a suitable parameter for large airway pulmonary function in the old adults. SVC-FVC > 0.02 L had a certain predictive value for SAD in the elderly.

Keywords Old people, Small airway dysfunction, Large airway, Parameters of lung function

*Correspondence:
Hui Chen
hchenNephro@hotmail.com
[1]Department of Geriatrics, Wenzhou Central Hospital of Zhejiang Province/The Second Affiliated Hospital of Shanghai University, Wenzhou 325000, Zhejiang, China
[2]Pulmonary Function Laboratory, Wenzhou Central Hospital of Zhejiang Province/The Second Affiliated Hospital of Shanghai University, Wenzhou 325000, Zhejiang, China
[3]Department of Nephrology, Wenzhou Central Hospital of Zhejiang Province/The Second Affiliated Hospital of Shanghai University, Wenzhou 325000, Zhejiang, China

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases of the respiratory system, with a prevalence of COPD as high as 13.7% in people over 40 years old in China [1]. The latest research shows that COPD has become the third leading cause of death among Chinese residents in 2017 [2], and it is estimated that 5.4 million people may die from COPD and its related diseases every year by 2060 [3, 4]. Chronic respiratory diseases have seriously endangered people's health and brought a huge economic burden to families and society. It is of great significance to diagnose and intervene early to reduce the risk of onset and delay the progression of COPD.

Occupational dust and harmful gases are most likely to invade small airways, which mainly contribute to airway obstruction and airflow limitation [5]. Studies have shown that small airway dysfunction (SAD) occurs in all stages of COPD and exists in high-risk smokers who do not meet the diagnostic criteria for COPD [6, 7]. A cross-sectional study showed that SAD occurred in more than 90% of asthmatic patients [8]. A study from China included 50,479 patients with valid pulmonary function tests (PFTs) from 10 provinces using a multi-stage stratified sampling method and found that the total prevalence of SAD was as high as 43.5%, indicating that SAD is a common but neglected breathing abnormality [9]. Although the research on the detection and evaluation methods and clinical application of SAD has gradually become a hot spot in recent years [10, 11], there are few reports at home and abroad on whether SAD has a quantitative effect on the related parameters of large airway function in the early stage.

Therefore, this study aimed to retrospectively explore the correlation between simple SAD and the related parameters of large airway function in old people and the way SAD affects the related parameters of large airway function, to remind clinicians to pay attention to the necessity of PFTs in asymptomatic healthy people undergoing a check-up, and better promote the early diagnosis, prevention, and treatment of chronic respiratory diseases.

Patients and methods

Study patients

A total of 15,129 elderly patients who had completed a full set of PFTs in the Outpatient Department (including the Health Examination Center) and Inpatient Department of Wenzhou Central Hospital from January 2016 to December 2022 were selected. The inclusion criteria were as follows: (1) patients aged 60 to 80 years; (2) patients with body mass index (BMI) ranging from 17 to 28 kg/m^2; (3) patients with normal blood routine, biochemical indexes, and electrocardiogram (ECG); (4) patients with no history of chronic diseases of cardiovascular, respiratory, neuromuscular, and other systems; (5) patients with complete pulmonary function data had the measured/predicted values of forced expiratory capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow (PEF) ≥ 80% and FEV1/FVC ≥ 70%. The exclusion criteria were: (1) patients with a history of acute respiratory infection within 2 weeks; (2) patients unable to finish the examination or unable to obtain the correct data; (3) patients with abnormal flow-volume and volume-time loops; (4) patients with exposure to dust or other irritating and harmful gases; (5) patients with β-2 agonists, theophylline, anticholinergics within 24 h and glucocorticoids within 72 h before examination; (6) patients with suspected disorders of the large airway or upper airway obstruction syndrome. This study was approved by the Ethics Committee of Wenzhou Central Hospital (No. 2020-04-006), and all patients gave informed consent. All methods were performed in accordance with the relevant guidelines and regulations. A clinical trial number is not applicable to this study.

Measurements

PFTs

All patients underwent spirometry (Jaeger MasterScreen, CareFusion Germany 234 GmbH, Germany). Before data collection, the instrument was calibrated for each participant by a skilled technician. Age, gender, height, and BMI were collected. At least 3 acceptable tests were taken with a variation of < 5% or a difference of < 150 ml between the two FVC tests and expiration time > 6 s or > expected expiration time. The optimal pulmonary function-related parameters including slow vital capacity (SVC), FVC, FEV_1, FEV_1/FVC, PEF, forced expiratory flow after 25% of vital capacity (FEF25 or MEF75), forced expiratory flow after 50% of vital capacity (FEF50 or MEF50), forced expiratory flow after 75% of vital capacity (FEF75 or MEF25), and maximal mid-expiratory flow (MMEF) were measured. Total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), RV/TLC, diffusion capacity for carbon monoxide (DLCO), and specific diffusing capacity (KCO) were measured according to the standardization of the measurement of single-breath DLCO (DLCOsb). The procedure was performed following the American Thoracic Society and European Respiratory Society (ATS/ERS) [12, 13].

Grouping

According to the inclusion and exclusion criteria, all finally included patients were divided into control and observation groups primarily based on the measured/predicted values of MEF50, MEF25, and MMEF. The specific grouping criteria were: (I) the control group: (1) the measured/predicted values of MEF50, MEF25, and

Table 1 Characteristics between the observation group and the control group

Variables	Observation group ($n=104$)	Control group ($n=102$)	χ^2/t/U	*P*
Gender			0.018	0.892
Male	54	52		
Female	52	50		
Age, years, mean ± SD	66.92 ± 4.76	65.75 ± 4.46	4550	0.077
Height, cm, mean ± SD	160.76 ± 7.11	160.72 ± 6.90	0.045	0.964
Weight, kg, mean ± SD	60.35 ± 9.42	60.77 ± 9.02	0.332	0.740
BMI, kg/m^2, mean ± SD	23.28 ± 2.81	23.46 ± 2.63	5100.5	0.634

SD: standard deviation; BMI: body mass index

MMEF were ≥ 70%; (2) patients with no known smoking history; (3) patients with normal chest computerized tomography (CT); (II) the observation group: (1) there were more than 2 measured/predicted values in MEF50, MEF25, and MMEF < 65% [14]; (2) no restrictions on patients' smoking history; (3) patients with normal chest CT or SAD-related imaging (e.g., lobular central emphysema). Finally, 104 elderly patients with SAD (the observation group) and 102 elderly patients with normal pulmonary function (the control group) were selected.

Pulmonary function parameters

The parameters of large airway function included SVC, FVC, FEV_1, PEF, and MEF75. MEF75 was used as one of the diagnostic parameters of SAD by ATS/ERS [15]. However, given that MEF75 was a flow parameter reflecting early expiration and was more sensitive to large airway obstruction, it was included in the analysis of parameters of large airway function in this study. Maximal voluntary ventilation (MVV) was not included in the analysis because of the high requirements and long duration of the test, and the elderly patients in this study were prone to incomplete data or poor reliability. The parameters of static pulmonary function included TLC, FRC, RV, RV/TLC, DLCO, and KCO. The parameters of small airway function include MEF50, MEF25, and MMEF. The derived measures included the difference of vital capacity (SVC-FVC) and vital capacity ratio (FVC/SVC).

Statistical analysis

SPSS 20.0 software (IBM Corporation, Armonk, NY, USA) was used to statistically analyze the data. Measurement data consistent with normal distribution were expressed as $x \pm s$. The independent sample t-test was used for comparison between the two groups. Mann-Whitney U test was used to compare the means of non-normal distribution variables. Count data were expressed as the number of cases or a percentage (%), and χ^2 test was used for comparison between groups. Pearson correlation was used for analysis. The predictive value of SVC-FVC and FVC/SVC for SAD was analyzed by the area under the receiver operating characteristic curve (AUC), and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

No significant differences were observed in gender, age, height, weight, and BMI between the observation group and the control group ($P > 0.05$) (Table 1).

Correlation between the parameters of small airway function and the parameters of large airway function in observation group and control group

The parameters of small airway function including MEF50, MEF25, and MMEF were positively correlated with SVC, FVC, FEV_1, PEF, and MEF75 in the large airway in the two groups ($r = 0.280$–0.634, $P < 0.01$). Except for MEF25 in the control group was weakly correlated with FEV_1/FVC ($r = 0.227$, $P < 0.05$), the other parameters did not correlate with FEV_1/FVC ($P > 0.05$) (Table 2).

Comparison of the parameters of large airway function in the observation group and control group

Except for PEF ($P > 0.05$), the other 5 parameters in the observation group were significantly different between the two groups ($P < 0.05$) (Table 3).

Table 2 Correlation between the parameters of small airway function and the parameters of large airway function in the two groups

Variables	Observation group			Control group		
	MEF50	MEF25	MMEF	MEF50	MEF25	MMEF
SVC	0.430^{***}	0.433^{***}	0.541^{***}	0.581^{***}	0.350^{***}	0.569^{***}
FVC	0.458^{***}	0.479^{***}	0.601^{***}	0.597^{***}	0.346^{***}	0.576^{***}
FEV_1	0.563^{***}	0.560^{***}	0.696^{***}	0.651^{***}	0.459^{***}	0.672^{***}
FEV_1/FVC	0.143	0.046	0.024	-0.147	0.227^{*}	0.026
PEF	0.411^{***}	0.421^{***}	0.508^{***}	0.490^{***}	0.280^{**}	0.493^{***}
MEF75	0.613^{***}	0.369^{***}	0.573^{***}	0.634^{***}	0.322^{***}	0.613^{***}

SVC: slow vital capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; PEF: peak flow; MEF75, MEF50, and MEF25: maximal flows at 75%, 50% and 25% of remaining forced vital capacity; MMEF: maximum mid-expiratory flow.

$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

Table 3 Comparison of the parameters of large airway function in observation group and control group

Variables	Observation group ($n=104$)	Control group ($n=102$)	t/U
SVC, L, mean ± SD	2.87 ± 0.63	3.10 ± 0.66	2.496*
FVC, L, mean ± SD	2.79 ± 0.64	3.06 ± 0.66	2.958**
FEV_1, L, mean ± SD	2.11 ± 0.42	2.51 ± 0.47	6.437***
FEV_1/FVC, %, mean ± SD	76.38 ± 4.43	82.79 ± 4.07	10.815***
PEF, L, mean ± SD	6.22 ± 1.34	6.47 ± 1.35	1.340
MEF75, L, mean ± SD	5.04 ± 1.02	5.93 ± 1.15	2939.5***

SD: standard deviation; SVC, slow vital capacity; FVC, forced vital capacity; FEV_1 denotes forced expiratory volume in 1 s; PEF, peak flow; MEF75 denotes maximal flows at 75% of remaining forced vital capacity.

*$P<0.05$; **$P<0.01$; ***$P<0.001$

Table 4 Comparison of static pulmonary function test parameters between the two groups

Variables	Observation group ($n=104$)	Control group ($n=102$)	t/U
TLC, L, mean ± SD	4.70 ± 0.81	4.80 ± 0.86	0.821***
FRC, L, mean ± SD	2.80 ± 0.73	2.66 ± 0.65	1.366***
RV, L, mean ± SD	2.13 ± 0.43	1.99 ± 0.46	2.235*
RV/TLC, %, mean ± SD	45.50 ± 5.91	41.67 ± 6.29	4.512***
DLCO, mmol•min^{-1}•kPa^{-1}, mean ± SD	5.59 ± 1.18	6.49 ± 1.18	5.498***

SD: standard deviation; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; DLCO: diffusion capacity for carbon monoxide.

*$P<0.05$; ***$P<0.001$

Comparison of static pulmonary function test parameters between the observation group and the control group

There was no significant difference in TLC and FRC ($P>0.05$), but there were significant differences in RV, RV/TLC, DLCO, and KCO ($P<0.001$) between the two groups (Table 4).

SVC-FVC and FVC/SVC

There were 66 cases of SVC-FVC > 0 (FVC/SVC < 1) (66/104, 63.46%) in the observation group) and 45 cases of the control group (45/102, 44.12%), with a statistically significant difference between the two groups ($\chi^2=7.754$, $P=0.005$). The AUC of SVC-FVC and FVC/SVC in the prediction of SAD was 0.631 and 0.639, respectively, with a sensitivity and specificity of 63% ($P=0.001$) (Table 5).

Discussion

The results of this study showed that parameters of small airway function including MEF50, MEF25, and MMEF were positively correlated with SVC, FVC, FEV_1, PEF, and MEF75 in the large airway in the two groups ($P<0.01$), MEF25 in the control group had a weak correlation with FEV_1/FVC in the observation group ($r=0.227$, $P<0.05$), and other parameters did not correlate with FEV_1/FVC ($P>0.05$), indicating that there was a certain correlation between the parameters of large and small airway function in both normal people and SAD patients, but there was no correlation between the parameters of small airway function and FEV_1/FVC. This phenomenon has not been reported in the literature so far. The absence of correlation between MEF50, MMEF, and FEV_1/FVC in the two groups may be due to the correlation being offset by FEV_1/FVC. Stockley et al. [16] reported that MMEF was significantly correlated with FEV_1/FVC, but the decline rate of MMEF with the progression of the disease was much greater than that of FEV_1/FVC. MMEF is one of the most commonly used clinical parameters to evaluate SAD [14]. However, due to its large variation rate [17], little correlation with RV/TLC [18], and high dependence on the accuracy of FVC measurement [19], AST did not support it as a parameter of SAD in pulmonary function guidelines. There were few reports on the correlation between MEF50, MEF25, and the parameters of large airway function.

In this study, the elderly patients with SAD (all the parameters of large airway function were in the normal range) were compared with elderly patients with normal lung function (all the parameters of small airway function and large airway function were in the normal range). It was found that SVC, FVC, FEV_1, FEV_1/FVC, and MEF75 in the observation group were significantly lower than those in the control group, indicating that SAD has had corresponding effects on the parameters of the large airway function, but only in the process of quantitative change, not yet in the stage of qualitative change (that was, meeting any of the following criteria: the actual/predicted values of FVC < 80%; the actual/predicted values of FEV_1 < 80%; FEV_1/FVC < 0.7 [20]). PEF was the only parameter of large airway function in this study that showed no difference between the two groups. PEF refers to the instantaneous flow at the peak expiratory flow rate during the measurement of FVC, which is mainly related to the strength of respiratory muscles, the presence or absence of airway obstruction, and many other factors.

Table 5 The predictive performance of SVC-FVC and FVC/SVC

Variables	AUC (95% CI)	SE	*P*	Optimal cut-off value	Sensitivity	Specificity
SVC-FVC	0.631 (0.555, 0.707)	0.039	0.001	0.02	0.63	0.63
FVC/SVC	0.639 (0.563, 0.714)	0.039	0.001	0.99	0.64	0.63

SVC: slow vital capacity; FVC: forced vital capacity; AUC: area under curve; CI: confidence internal; SE: standard error

PEF, significantly different from FEV_1, can be achieved during the first 100 milliseconds of a patient initiating breath [21]. PEF is clinically used to measure large airway function and respiratory muscle strength, and PEF variation rate is mainly used in the diagnosis and monitoring of bronchial asthma [22]. The concept of PEF shows that PEF is more related to the instantaneous power of respiratory muscles. Old people are a special group, and instantaneous power is more difficult to achieve because respiratory muscle strength decreases year by year with age. Therefore, even if SAD existed, there was no difference in PEF. Therefore, it was believed that PEF may not be suitable as a parameter to reflect the large airway function in elderly patients, which needs to be confirmed by further multicenter and prospective clinical studies.

The mechanism by which SAD affects large airway function is not clear, but the possible factors are as followed. Firstly, the common causes of SAD are infection, smoking, occupational exposure to harmful particles or gases, and allergies, which may also lead to disorders of the large airway. Secondly, SAD and emphysema are also closely related [23]. RV/TLC is one of the main pulmonary function diagnostic indicators of emphysema and gas trapping and is more sensitive than imaging, although not as visual as emphysema imaging. This study suggested that the RV/TLC and FRC in the observation group was significantly higher than that in the control group, indicating that SAD patients may have emphysema and gas trapping or both, which led to the decline of alveolar elastic retraction force, and eventually led to the decline of large airway parameters. Thirdly, SAD was associated with interstitial lung abnormalities (ILA), resulting in decreased lung compliance, and indirectly affecting the results of large airway function tests. Washko et al. [24] performed an HRCT examination on 2,416 smoking patients, finding that 35.6% of the selected cases had ILA. DLCO and KCO in the observation group were significantly lower than those in the control group, which also confirmed the dysfunction of pulmonary gas exchange in elderly patients with SAD. Fourthly, this study found that in the elderly patients, SAD alone did not affect TLC and FRC, but brought increased RV and decreased expiratory reserve volume (ERV), thereby reducing SVC and FVC.

Vital capacity can be divided into SVC and FVC. The difference between SVC and FVC is that SVC is not limited by expiratory time. SVC and FVC are equal in people without airway obstruction. If airway obstruction is present, FVC < SVC. Therefore, an increased SVC-FVC [25, 26] and a decreased FVC/SVC [27] are potential markers of SAD, but standard reference values are currently lacking. There were 66 cases of SVC-FVC > 0 (FVC/SVC < 1) (63.46%) in the observation group) and 45 cases of the control group (44.12%), and the difference between the two groups was statistically significant ($P = 0.005$), indicating that SVC-FVC and FVC/SVC were more sensitive than other parameters of large airway function. The AUC of SVC-FVC and FVC/SVC in the prediction of SAD was 0.631 and 0.639, respectively, with a sensitivity and specificity of 63%, indicating that the two parameters had certain predictive value, and the best cut-off point of SVC-FVC was 0.02 L. Cohen et al. [28] found that FVC/SVC decreased significantly with the progression of the disease in children with bronchiolitis obliterans syndrome, but it was not related to the change of FEV_1. They believed that FVC/SVC could be used to evaluate the change in small airway function and monitor the clinical condition.

The routine pulmonary ventilation function examination method was adopted in this study, and the abnormalities of the three small airway flow rate indexes were one of the main group indexes. Therefore, patients with small airway disease and emphysema may be included in the observation group of this study. Small airway disease and emphysema are closely related, and small airway instability has previously been attributed to small airway occlusion due to disruption of alveolar structure and lack of elastin fiber support, but this theory is predicated on the idea that alveolar disruption precedes and SAD follows. McDonough et al. [23] proposed the narrowing and disappearance of small conducting airways before the onset of emphysematous destruction, and they thought that emphysema was caused by the collapse of alveolar walls due to the loss of the support of distal small airways. If their hypothesis is true, it would indicate that emphysema is part of small airway diseases, but this needs to be confirmed by further longitudinal clinical studies. These illustrate the interplay between emphysema and small airway disease, and may even be manifestations of the same disease at different stages of development. Therefore, even if there are some emphysema patients in the observation group of our study, it still does not affect the research conclusion that SAD alone can produce quantitative changes in indicators related to the large airways, but emphysema may affect the degree of quantitative changes. In addition, the use of a control group in this study could eliminate the influence of age-related physiological emphysema in the elderly on the results.

There are some limitations in this study. A retrospective investigation of medical records may cause clinical bias. High-Resolution CT (HRCT) and large airway-related imaging were not used in chest examination. Upper airway syndrome was excluded only by a return visit, without head & neck system (ENT) consultation or corresponding auxiliary examination. In addition, the observation group was not subgrouped according to the presence or absence of concomitant emphysema to assess the impact of emphysema on the results of this study.

Conclusion

In conclusion, SAD in old people had a certain degree of influence on the parameters of large airway function. PEF may not be suitable as a parameter reflecting large airway function in old people. SVC-FVC > 0.02 L had a certain predictive value for SAD in the old people.

Abbreviations

COPD	Chronic obstructive pulmonary disease
SAD	Small airway dysfunction
PFTs	Pulmonary function tests
BMI	Body mass index
FVC	Forced expiratory capacity
SVC	Slow vital capacity
PEF	Peak expiratory flow
FEF25/MEF75	Forced expiratory flow after 25% of vital capacity
FEF50/MEF50	Forced expiratory flow after 50% of vital capacity
MMEF	Maximal mid-expiratory flow
TLC	Total lung capacity
FRC	Functional residual capacity
RV	Residual volume
DLCO	Diffusion capacity for carbon monoxide
KCO	Specific diffusing capacity
DLCOsb	Single-breath DLCO
MVV	Maximal voluntary ventilation

Acknowledgements
Not applicable.

Author contributions
HC and JP designed the study. JP wrote the manuscript. JP, YZ, and WL collected, analyzed, and interpreted the data. HC critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript.

Funding
This research was supported by the Science and Technology Project of Wenzhou (No. Y20240225).

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Wenzhou Central Hospital (No. 2020-04-006), and all patients gave informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 June 2024 / Accepted: 10 April 2025
Published online: 22 April 2025

References

1. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China pulmonary health [CPH] study): a National cross-sectional study. Lancet (London England). 2018;391:1706–17.
2. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the global burden of disease study 2017. Volume 394. London, England: Lancet; 2019. pp. 1145–58.
3. Global initiative for chronic obstructive lung disease. Global strategy for Zhe diagnosis,management,and prevention of chornic obstructive pulmonary disease. REPORT); 2021.
4. Chronic Obstructive Pulmonary Disease Committee, Respiratory Society, Chinese Medical Association. Working committee on chronic pulmonary obstructive disease, Chinese association of respiratory physicians. Guidelines for diagnosis and treatment of chronic obstructive pulmonary disease (2021 revision). Chin J Tuberculosis Respiratory Dis. 2021;44:170–205.
5. Piorunek T, Kostrzewska M, Stelmach-Mardas M, Mardas M, Michalak S, Goździk-Spychalska J, et al. Small airway obstruction in chronic obstructive pulmonary disease: potential parameters for early detection. Adv Exp Med Biol. 2017;980:75–82.
6. Crisafulli E, Pisi R, Aiello M, Vigna M, Tzani P, Torres A, et al. Prevalence of Small-Airway dysfunction among COPD patients with different GOLD stages and its role in the impact of disease. Respir Int Rev Thorac Dis. 2017;93:32–41.
7. Bell AS, Lawrence PJ, Singh D, Horsley A. Feasibility and challenges of using multiple breath washout in COPD. Int J Chronic Obstr Pulm Dis. 2018;13:2113–9.
8. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respiratory Med. 2019;7:402–16.
9. Xiao D, Chen Z, Wu S, Huang K, Xu J, Yang L, et al. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a National cross-sectional study. Lancet Respiratory Med. 2020;8:1081–93.
10. Knox-Brown B, Mulhern O, Amaral AFS. Spirometry parameters used to define small airways obstruction in population-based studies: systematic review protocol. BMJ Open. 2021;11:e052931.
11. Li Y, Li XY, Yuan LR, Wang HL, Pang M. Evaluation of small airway function and its application in patients with chronic obstructive pulmonary disease (Review). Experimental Therapeutic Med. 2021;22:1386.
12. Pellegrino R, Viegi G, Brusasco V, Burgos F, Casaburi R, Coates A, et al. ATS/ERS task force:interpretative Str ategies for lung function tests. Eur Respir J. 2005;26:948–68.
13. Macintyre N, Crapo RO, Viegi G, Johnson DC, Wanger JI. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720–35.
14. Pulmonary Function Group CRS. Guidelines for pulmonary function testing (Part 2)- spirometry. Chin J Tuberculosis Respiratory Dis. 2014;37:481–6.
15. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med. 2019;200:e70–88.
16. Stockley JA, Ismail AM, Hughes SM, Edgar R, Stockley RA, Sapey E. Maximal mid-expiratory flow detects early lung disease in α(1)-antitrypsin deficiency. Eur Respir J. 2017; 49.
17. Burgel P. The role of small airways in obstructive airway diseases. Eur Respir Rev. 2011;20:23–33.
18. Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF et al. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. Journal of applied physiology (Bethesda, Md: 1985). 2008; 104: 394–403.
19. Mirsadraee M, Boskabady MH, Attaran D. Diagnosis of chronic obstructive pulmonary disease earlier than current global initiative for obstructive lung disease guidelines using a feasible spirometry parameter (maximal-mid expiratory flow/forced vital capacity). Chronic Resp Dis. 2013;10:191–6.
20. Sorli-Aguilar M, Martin-Lujan F, Flores-Mateo G, Arija-Val V, Basora-Gallisa J, Sola-Alberich R. Dietary patterns are associated with lung function among Spanish smokers without respiratory disease. BMC Pulm Med. 2016;16:162.
21. Dai YR. Clinical application of pulmonary function testing in Airway diseases (1st edition). Beijing: people's medical publishing house. 2013; 10: 60– 3.
22. Pulmonary Function Group, Chinese Respiratory Society. Guidelines for pulmonary function testing - peak expiratory flow and rate of variation. Chin J Tuberculosis Respiratory Dis. 2017;40:426–30.
23. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med. 2011;365:1567–75.

24. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011;364:897–906.
25. Chhabra SK. Forced vital capacity, slow vital capacity, or inspiratory vital capacity: which is the best measure of vital capacity? J Asthma: Official J Association Care Asthma. 1998;35:361–5.
26. Chan ED, Irvin CG. The detection of collapsible airways contributing to airflow limitation. Chest. 1995;107:856–9.
27. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med. 1999;160:1001–8.
28. Cohen J, Postma DS, Vink-Klooster K, van der Bij W, Verschuuren E, Ten Hacken NH, et al. FVC to slow inspiratory vital capacity ratio: a potential marker for small airways obstruction. Chest. 2007;132:1198–203.

Publisher's note