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Value of CT three-dimensional imaging combined with FEV3 and FEV6 in evaluating small airway lesions in asthma

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Abstract

The main symptoms of asthma include thickening of the airway wall and constriction of the airways. Peak expiratory flow and spirometry are commonly employed in diagnosing and treating asthma. The forced expiratory volume in 6 seconds (FEV6) and the forced expiratory volume in 3 seconds (FEV3) were assessed in this study. Its connection to structural alterations in the airways is unclear, however. We aim to examine the connection between 3D CT scans and asthma spirometry. Using 3D computed tomography, the wall area (WA) and internal airway area (Ai) of third- to sixth-generation bronchi were assessed in asthmatic individuals. In 50 asthmatic patients, the associations between asthma and age, height, weight, BMI, length of disease, FEV3, FEV6, FEV1/FEV3, FEV1/FEV6, and FVC were assessed. Data analysis was done using a chi-square test. WA/BSA was significantly correlated in third, fourth, fifth, and sixth-generation bronchi ($p < 0.001$). Partial rank correlation analysis showed that spirometry was non-significantly associated with bronchial WA/BSA. In contrast, there was no correlation between spirometry and 3D CT scan. Spirometry cannot be used as a substitute for asthma assessment.

Key word: CT, 3D imaging, FEV3, FEV6, Asthma

Introduction

Airway diseases, particularly asthma, are among the most prevalent health conditions globally. Over the past two decades, asthma has shown a significant increase in incidence in many countries, now affecting roughly 10% of the population in most industrialized nations. This rise in prevalence places a substantial economic burden on society, encompassing both direct healthcare costs and indirect expenses, such as lost productivity and long-term care requirements [1] .Asthma is a chronic respiratory condition characterized by a person's reduced ability to breathe freely. This impairment is primarily due to inflammation, structural changes, and

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mucus buildup in the airways, all of which play critical roles in the onset and progression of the disease . Even minor airway abnormalities can significantly increase the likelihood of developing asthma. Clinically, asthma is manifested by symptoms such as coughing, chest tightness, wheezing, and shortness of breath (dyspnea) [2, 3]. However, conventional imaging techniques often fall short in detecting the subtle airway anomalies that contribute to asthma. While clinical assessment remains the cornerstone of asthma diagnosis and management, pulmonary function tests (PFTs) are commonly used to assess lung function and gauge the severity of the disease. These tests provide valuable insights but may not always capture the full extent of airway pathology, particularly in the early stages [4].

Computed tomography (CT) imaging is a highly valuable, non-invasive technique used to obtain detailed and comprehensive information about lung structure, including the smallest airways. By employing three-dimensional (3D) imaging techniques, CT scans can provide a complete visualization of the entire airway tree, from the larger central airways to the smaller peripheral branches [5, 6] .One of the key advantages of 3D CT imaging is its ability to assess the thickness of airway walls and detect potential structural abnormalities. This capability is crucial for diagnosing conditions such as bronchiectasis, which is characterized by the chronic dilation and thickening of the walls of the respiratory passages . Additionally, CT imaging plays a vital role in evaluating various pathological changes in the airways, such as the presence of tumors or inflammatory lesions . This detailed imaging allows for earlier and more accurate diagnosis and management of airway diseases [7, 8].

The presence of lesions affecting the functionality of the small airways is a critical factor in the development and progression of asthma symptoms. These lesions can include a range of abnormalities such as inflammation, fibrosis (the excessive buildup of scar tissue), and mucus accumulation within the airway walls. When these factors occur simultaneously, they can lead to significant airflow restriction, resulting in a decrease in pulmonary function [8, 9]. Inflammation within the bronchioles is a hallmark feature of asthma. The inflammatory processes can cause edema (swelling) of the airway walls, leading to the constriction of the respiratory passages. This constriction restricts airflow, making it more difficult for individuals with asthma to breathe. Additionally, the progression of fibrosis, which involves the accumulation of collagen and other connective tissue components, can further contribute to airway constriction and obstruction. Fibrotic lesions in the small airways reduce their elasticity and increase their rigidity, which exacerbates the difficulty of airflow (Figure 1) [10-12].

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Moreover, mucus accumulation within the small airways can significantly worsen airflow restriction. Excessive mucus production is a common feature of asthma and contributes to the blockage of the respiratory passages. When mucus accumulates, it intensifies the existing airflow obstruction. The combined effects of inflammation, fibrosis, and mucus buildup create a challenging environment for proper airflow, which adversely impacts pulmonary function [13, 14].

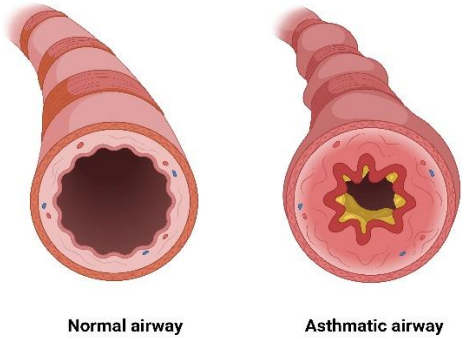

Figure 1. Comparison of asthmatic airway and normal airway

The FEV3 (Forced Expiratory Volume in 3 seconds) and FEV6 (Forced Expiratory Volume in 6 seconds) tests are valuable tools for assessing pulmonary function, particularly in evaluating airflow restriction and obstruction in the small airways. These measurements provide important indicators of respiratory health and help healthcare practitioners understand the extent of airway involvement in individuals, especially those with asthma [15]. FEV3 stands for Forced Expiratory Volume in three seconds. It measures the volume of air expelled from the lungs during the first three seconds of a forced vital capacity maneuver. This measurement is crucial for detecting early signs of airflow limitation and obstruction in the smaller airways. By analyzing the volume of air exhaled within this short period, healthcare practitioners can identify potential irregularities and gauge the involvement of the small airways in respiratory issues [16, 17]. FEV6, in contrast, measures the Forced Expiratory Volume over the entire duration of a forced vital capacity maneuver, which is typically six seconds. This measurement provides the total volume of air expelled from the lungs throughout the complete exhalation cycle. FEV6 offers a comprehensive evaluation of pulmonary function, including both larger and smaller airways. This broader assessment allows healthcare practitioners to determine overall pulmonary function and identify significant airflow restriction or obstruction across the entire respiratory cycle [18, 19].

Therefore, this study aimed to examine the connection between 3D computed tomography (CT) scans and spirometry in assessing asthma, specifically focusing on the wall area (WA) and internal airway area (Ai) of third- to sixth-generation bronchi in asthmatic individuals. The study aims to determine the associations between these structural airway measurements and various spirometric parameters, including FEV3, FEV6, FEV1/FEV3, FEV1/FEV6, and FVC, in order to evaluate the effectiveness of spirometry as a tool for asthma assessment.

Subjects and Methods

Subjects

This study, conducted at Huashan Hospital in China from May 2022 to October 2023, is a cross-sectional, descriptive, and analytical investigation involving 55 asthmatic patients aged 18 to 85, with an average age of 35.43 (Table 1). The participants were selected based on the American Thoracic Society's definition of asthma, ensuring that none had experienced a worsening illness or smoked at least a month before the trial. Following the selection of patients for the study, informed consent was obtained to ensure their voluntary participation. Each patient's case and paraclinical findings were meticulously reviewed by a trained general practitioner and a medical imaging specialist, ensuring comprehensive data collection. Five individuals with respiratory motor problems were excluded. The severity of asthma among the participants was classified according to the Global Initiative for Asthma (GINA) standards, resulting in 30 patients with mild asthma, 10 with stable asthma, and 10 with moderate and stable asthma. This classification aimed to provide a comprehensive understanding of asthma severity within the study group, potentially aiding in the development of more effective management strategies for asthmatic patients.

Table 1. Patient profile

Variables	Min	Max	Mean	SD
Age (year)	18	85	35.43	10.23
Weight (Kg)	45	103	76.28	14.27
Height (cm)	148	180	166.23	6.21
BMI (Kg/m2)	13.02	35.26	25.36	4.53
Duration of asthma, years	3	28	19.45	5.62

SD, Standard deviation; BMI, Body mass index

Assessment of asthma through spirometry

Spirometry was conducted for all participants using a flow-type spirometer (Spirolab III, MIR, Italy) in our respiratory laboratory under standardized conditions, including a sitting position, body temperature, and saturated pressure in the morning. The tests were administered by an occupational medicine assistant, ensuring consistency and

accuracy. The spirometer used is automatically calibrated, enhancing the reliability of the measurements. Key spirometric parameters assessed included FEV3, FEV6, FEV1/FEV3, and FEV1/FEV6 ratios, which provide insights into the patients' lung function. Additionally, Forced Vital Capacity (FVC) was evaluated in all patients, offering a comprehensive assessment of their respiratory health. These measurements are crucial for diagnosing and monitoring asthma, as they help determine the severity and progression of the disease.

Dimensional analysis of airways

In this study, individuals underwent scanning using a 3D X-ray microscopic CT scanner (TDM-1000) while lying supine, with the scans performed during complete inspiration and breath-holding. Prior to the scans, participants were thoroughly instructed on breath-holding techniques to ensure consistency. The TDM-1000 scanner was set with a rotation time of 0.5 seconds, a tube current ranging from 0 to 250 μA, and a focus point of 5 μm. The images were reconstructed using a standard procedure with a reconstruction distance of 0.5 mm and a slice thickness of 1 mm. The reconstruction data were then imported into a workstation to create a three-dimensional model of the bronchial tree. Measurements were taken of the body surface area (BSA)-corrected wall area (WA) and internal airway area (Ai) of the third- to sixth-generation bronchi, using the 3D CT images. These measurements, WA/BSA and Ai/BSA, provided detailed insights into the bronchial structure, allowing for precise analysis of the airway dimensions relative to the body surface area. This method offers a comprehensive approach to studying the bronchial tree, potentially aiding in the diagnosis and understanding of various respiratory conditions.

Statistical analysis

SPSS software (version 21) was used for statistical analysis. Descriptive statistics were provided to summarize the data, and further analysis was conducted using Kayasquare statistical tests at a significance level of $\alpha=0.05$. This rigorous process aimed to ensure the reliability and validity of the study's findings, contributing valuable insights into the characteristics and severity of asthma among the participants.

Results

Spirometry analysis

The spirometry results, detailed in Table 2, include measurements of FEV1, FEV3 , FEV6 , and FVC. These parameters were assessed across four different registrations, providing a comprehensive overview of lung function. Additionally, the ratios of FEV1 to FEV3 and FEV1 to FEV6 were calculated, offering further insights into the patients' respiratory efficiency. The significance of these measurements is particularly notable in patients with asthma, as indicated in the table. Asthma patients often exhibit reduced values in these spirometric indices due to airway obstruction, which can be quantified through these tests. The FEV1/FVC ratio, in particular, is a critical marker for diagnosing obstructive lung diseases like asthma. By comparing these ratios and absolute values, clinicians can better understand the severity and progression of asthma in patients, enabling more tailored and effective treatment plans. This detailed analysis underscores the importance of spirometry in diagnosing and managing asthma, highlighting the utility of these specific measurements in clinical practice. In addition

there is no significance in any modes and P>0.05 for all modes.

Table 2. Spirometry analysis for measurements of FEV1, FEV3 , FEV6 , and FVC.

	Min	Max	Mean	SD	P value
FEV_1 (ml)	970	4670	2627.65	1070.27	<0.001
FEV_3 (ml)	1528	6310	3675.98	1502.77	<0.001
FEV_6 (ml)	1863	6990	4099.76	1400.45	<0.01
FVC (ml)	2000	7140	4177.80	1365.30	<0.001
FEV1/FEV3	54	94	74.66	11.12	<0.001
FEV1/FEV6	43.20	94.30	77.91	8.76	<0.001

SD, Standard deviation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity

Three-dimensional CT analysis of the airways

In this study, machine learning algorithms were employed to identify all potential airway candidates, which were then used to create an airway centerline through a minimal spanning tree approach (Table 3). The graph cuts method was applied to automatically extract the inner and outer shapes of the airways, with manual corrections made if any errors occurred during this process. Measurements were taken from six specific bronchi (B1, B2, B3, B8, B9, and B10) in the right lung. One of the authors, who was blinded to the patients' information, conducted the analysis to ensure unbiased results. The study focused on four layers of the airways: the third (segmental), fourth (sub-segmental), fifth, and sixth generation bronchi for each selected bronchus. The wall area (WA) was defined as the region between the inner and outer edges of the airway. Each participant had a total of 24 images, with six images taken at each bronchial level. The results for each bronchial generation were reported as the mean of the six airways. To account for variations in body size among participants, the Ai and WA were normalized by BSA, resulting in the metrics Ai/BSA and WA/BSA. This normalization ensured that the measurements were not influenced by the individual body sizes of the patients, providing a more accurate comparison of

airway dimensions across the study population. This comprehensive approach allowed for detailed analysis of the bronchial structure, contributing valuable insights into respiratory health and potential abnormalities.

Table 3. Morphology assessed by three-dimensional CT analysis in asthma

	Third-generation bronchi			Fourth-generation bronchi			Fifth-generation bronchi			Sixth-generation bronchi		
	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean
Ai (mm^2)	13.8	48.3	26.6	4.5	18.1	8.2	1.9	10.8	5.2	1.2	6.1	3.1
Ai/BSA (mm^2/m^2)	8.3	31.3	20.2	2.7	10.8	3.1	1.3	6.4	3.1	0.6	4.1	1.9
WA (mm^2)	27.8	43.9	35.2	16.1	35.8	24.9	21.3	32.9	24.9	17.3	31.1	21.8
WA/BSA (mm^2/m^2)	17.1	29.7	23.3	11.1	25.1	15.8	12.7	20.7	15.8	11.3	19.7	13.9

Ai, airway inner luminal area; WA, wall area; BSA, body surface area.

The Table 4 presents p-values for various pulmonary function tests across different generations of bronchi, specifically the third, fourth, fifth, and sixth generations. For the third-generation bronchi, the p-values for FEV1, FEV3, FEV6, and FVC are 0.745, 0.356, 0.421, and 0.945, respectively, indicating no significant differences in these measurements. Similarly, the fourth-generation bronchi show p-values of 0.865 for FEV1, 0.354 for FEV3, 0.387 for FEV6, and 0.997 for FVC, again suggesting no significant differences. The fifth and sixth-generation bronchi have p-values of 0.473 and 0.399 for FEV1, 0.276 and 0.275 for FEV3, 0.264 and 0.286 for FEV6, and 0.453 and 0.567 for FVC, respectively, which also do not indicate significant differences. Additionally, the ratios of FEV1 to FEV3 and FEV1 to FEV6 for the third-generation bronchi have p-values of 0.654 and 0.631, respectively, while the fourth-generation bronchi have p-values of 0.354 and 0.387, respectively. These p-values suggest that there are

no statistically significant differences in the lung function measurements across the different generations of bronchi, implying that the airway dimensions and functionality remain consistent throughout these bronchial generations. This consistency is crucial for understanding the uniformity of airway structure and function in respiratory studies.

Table 4. p-values for various pulmonary function tests across different generations of bronchi, specifically the third, fourth, fifth, and sixth generations

	p-value of Third-generation bronchi	p-value of Fourth-generation bronchi	p-value of Fifth-generation bronchi	p-value of Sixth-generation bronchi
FEV_1 (ml)	0.745	0.865	0.473	0.399
FEV_3 (ml)	0.356	0.354	0.276	0.275
FEV_6 (ml)	0.421	0.387	0.264	0.286
FVC (ml)	0.945	0.997	0.453	0.567
FEV1/FEV3	0.654	0.354	0.487	0.435
FEV1/FEV6	0.631	0.387	0.483	0.455

Discussion

Asthma is characterized by airway constriction and bronchial wall thickening, which are critical for understanding its pathophysiology. While traditional diagnostic tools like peak expiratory flow and spirometry assess airflow restriction, they do not directly measure bronchial wall thickening, a significant aspect of asthma pathology [20]. Recent studies have explored advanced imaging techniques to better evaluate these structural changes. Research indicates that airway wall thickening is prevalent in asthmatic patients, with studies showing that 88.8% of children with severe asthma exhibit this condition on CT scans [21]. Metrics such as wall area percentage (WA%) and wall thickness (WT) have been linked to lung function, revealing that patients with thicker walls show greater sensitivity to asthma medications [22].

Magnetic Resonance Imaging (MRI)-UTE has emerged as a reliable, radiation-free alternative to CT for assessing bronchial dimensions, demonstrating good correlation with CT findings [23]. The ability to visualize and quantify bronchial wall thickening can enhance asthma management, allowing for tailored therapeutic approaches based on structural abnormalities [24]. Understanding the relationship between airway structure and function can lead to improved diagnostic criteria and treatment efficacy, particularly in severe cases. While these imaging advancements provide valuable insights into bronchial wall changes, the challenge remains in integrating these findings into routine clinical practice, as traditional spirometry continues to dominate asthma assessment [25].

CT scans significantly enhance diagnostic capabilities compared to standard X-rays, particularly in visualizing soft tissues and vascular structures. This advanced imaging technique is crucial for rapid assessment in emergency situations, providing detailed cross-sectional images that facilitate the identification of various medical conditions [26]. CT scans utilize advanced algorithms to reconstruct images based on X-ray attenuation, allowing for precise visualization of internal structures, including organs and blood vessels [27]. The technology is adept at detecting subtle injuries and conditions that standard X-rays may miss, particularly in soft tissues and complex anatomical regions [28]. In trauma cases, CT imaging has demonstrated 100% accuracy in diagnosing abdominal organ injuries, which is vital for timely intervention [29]. CT scans are integral in managing traumatic brain injuries, influencing critical treatment decisions and improving patient outcomes. While CT scans offer superior detail and speed, concerns about radiation exposure and the need for standardized protocols remain critical in ensuring patient safety and optimizing imaging practices [30].

The integration of anatomical data from CT imaging with functional assessments like FEV3 and FEV6 significantly enhances individualized treatment protocols for respiratory diseases. This multimodal approach not only aids in customizing therapies but also improves the monitoring of disease. CT imaging quantifies specific lung abnormalities, such as emphysema and airway wall thickening, allowing for tailored interventions in chronic obstructive pulmonary disease (COPD) patients [31]. Automated quantitative imaging methods can identify subtle changes in lung structure, which are crucial for developing personalized treatment strategies [32]. Longitudinal CT assessments can track changes in lung function and structure, providing insights into disease progression and treatment efficacy [33]. Techniques like parametric response mapping (PRM) enable detailed characterization of pulmonary pathologies, facilitating early detection of abnormalities and timely intervention [34].

Integrating 3D CT imaging with pulmonary function tests (PFTs) such as FEV3 and FEV6 allows for a complete assessment of major and minor airways in individuals with asthma. Pulmonary function tests (PFTs) provide quantitative assessments of lung function and are often used to evaluate respiratory disorders.With recent advances in imaging technology, quantitative CT analysis can provide detailed information on airway changes in lung diseases. CT analysis can non-invasively assess the airway internal lumen area and overall wall surface area in a

wide range of airway trees, which cannot be measured by spirometry [35].

According to previous works, this research showed that asthma can be detected through spirometry [36-38]. Langan et al. discussed how high-quality, office-based spirometry provides as valuable and reliable diagnostic information as testing performed in a pulmonary function laboratory. It highlights that spirometry is recommended as part of various medical societies' diagnostic workup for asthma [39]. Louis et al. emphasized the importance of spirometry with reversibility testing in diagnosing asthma. They also suggest considering other tests like nitric oxide measurement, peak expiratory flow variability, and bronchial challenge testing [40]. The study of Shin et al. explored the characteristics that can predict undiagnosed asthma in symptomatic adults, even when spirometry results are expected [41]. The systematic review of Carpenter et al. identified portable electronic spirometers capable of monitoring lung function and providing feedback to asthma patients. It underscores the role of spirometry in managing asthma [42]. In addition, Gallucci et al. discussed various tools for monitoring asthma, including spirometry, which provides objective measurements of lung function [43].

Due to the non-significance of the relationship between spirometry and CT scan, we cannot use spirometry as a substitute for 3D CT scan. Pulmonary function tests (PFTs), such as spirometry, are utilized to assess lung volumes and airflow, yielding significant insights into the functioning of the central airways. Nevertheless, it is essential to note that these tests may not comprehensively assess abnormalities in the narrow air passages, which are progressively acknowledged as significant factors in the manifestation of asthma symptoms and the advancement of the disease.

Conclusion

While spirometry, including measurements such as FEV3, FEV6, FEV1/FEV3, FEV1/FEV6, and FVC, is commonly used in diagnosing and managing asthma, it does not correlate significantly with structural alterations in the airways as assessed by 3D CT scans. Specifically, the WA and Ai of third- to sixth-generation bronchi, measured using 3D CT, showed significant correlations with BSA but not with spirometric parameters. This indicates that spirometry alone may not adequately reflect the structural changes in the airways of asthmatic patients. Therefore, the study suggests that 3D CT scans provide valuable additional information about airway morphology that spirometry cannot capture, highlighting the need for a more comprehensive approach to asthma assessment that includes imaging techniques alongside traditional spirometric tests.

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