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Mini Review

Ventilation Inhomogeneity, Risk and Severity of Pediatric Asthma

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Abstract

Ventilation inhomogeneity reflects the uneven distribution of air in the lungs and may be present in respiratory diseases. The two most studied methods for detecting inhomogeneity in children and adolescents are multiple breath washout with tracer gases and lung resonance with hyperpolarized gases. This review compiles the available evidence regarding the clinical utility of both methods for measuring the risk and severity of pediatric asthma.

Keywords: *Bronchial Asthma; Children; Adolescents; Ventilation Inhomogeneity*

Introduction

Ventilation inhomogeneity (VI) is the uneven or non-uniform distribution of gases within the lungs. In bronchial asthma, this phenomenon occurs because some peripheral airways are more collapsed than others, leading to a portion of alveolar compartments emptying faster with adequate time constant and good ventilation, while others will empty more slowly with a short time constant and poor ventilation [1,2]. Figure 1 shows a diagram representing the differences in the distribution of gases in the alveolar units resulting from variations in the time constant caused by the closure of the airway. In adults with asthma, VI has shown to correlate with greater severity of airflow obstruction, lower bronchodilator response, and could be useful in predicting response to biological treatments in patients with the high Th2 phenotype [3,4]. By contrast, in asthmatic children and adolescents, VI and its clinical application are less well known. This review aims to compile the evidence supporting the clinical utility of VI testing in pediatric asthma.

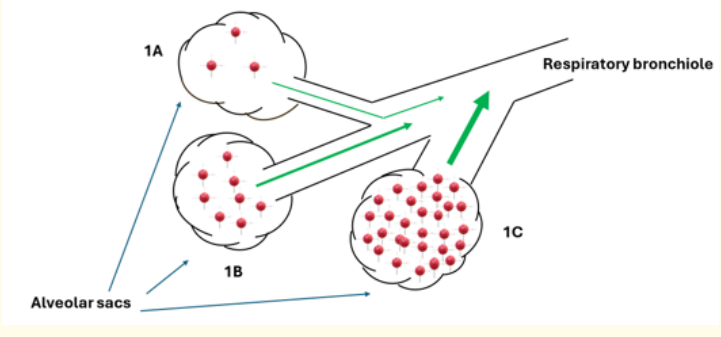

Figure 1: *Inhomogeneity of ventilation due to different time constants. 1A: Marked airway closure, long time constant, slow gas distribution. 1B: Mild airway closure, intermediate time constant and gas distribution. 1C: Normal airway, time constant, and gas distribution.*

Method

A review of the scientific evidence on the practicality of VI measurement in asthma in children and adolescents was conducted. The search for articles was conducted in July 2025 in the Medline (PubMed), Web of Science (WOS), EBSCO Host, Science Direct, and SCOPUS databases. MeSH terms and free terms in their English versions were used. The terms were grouped into two dimensions: (i) ventilation inhomogeneity or heterogeneity, and (ii) pediatric asthma. The Boolean operator "and" was used to integrate both dimensions. In addition, the abstracts of publications published at the American Thoracic Society (ATS) and European Respiratory Society (ERS) congresses were reviewed. The articles found were grouped into two topics: (1) VI and asthma risk, and (2) VI and asthma severity.

Methods used to measure ventilation inhomogeneity

Multiple breath washout (MBW) is a pulmonary function test used to measure volumes and regional distribution of lung ventilation and has global predictive values for individuals aged 2 to 81 years [5]. In MBW, an inert tracer gas is used, which can be endogenous (nitrogen) or exogenous (sulfur hexafluoride or helium) and is washed out by multiple tidal breaths, which allows its employment at early ages, when children have difficulty performing traditional tests such as spirometry [6]. For its correct interpretation, the MBW must have the technical requirements and standardization that allow eliminating leaks or changes in tracer gases [7]. In young children, variability in MBW results may increase, so care must be taken to ensure that the tidal volume is representative of age with variations of no more than 3 to 5%, use appropriate respiratory frequencies, and use equipment with well-synchronized software that allows viewing in real time the breathing pattern to detect pauses or fragmented breaths [8]. The lung clearance index (LCI) is the parameter of the MBW test that allows a global measurement of the heterogeneity of ventilation and represents the number of lung volume exchanges necessary to clear the tracer gas, which occurs when this gas drops to a concentration of 1/40 in respect to the initial one [9]. Figure 2 graphs the differences in tracer gas clearance in a normal subject and one with pulmonary disease with VI. The LCI can only demonstrate the overall VI, but does not allow to discern regional differences in VI. For such there are two additional indices, the first is called "Scond" and represents the VI generated in the conducting airway (first 16 bronchial generations), where the gas is transported by convection, and the second "Sacin" (17 to 23 bronchial generations) which reflects the VI produced in the acinar units where the gas is transported by diffusion [10].

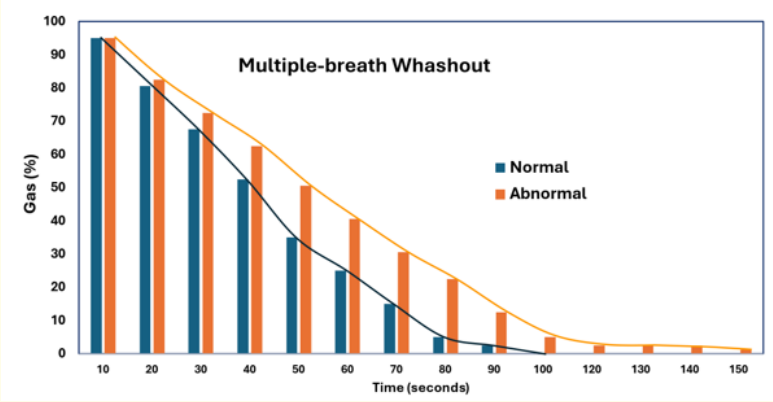

Figure 2: *Graph representing tracer gas concentration (Y axis) versus time in seconds (X axis). The blue bars show the time it takes for a normal individual to eliminate the tracer gas, and the orange bars show the time it takes for an individual with a lung disease that causes ventilation inhomogeneity.*

Another method for measuring VI that has had greater development in recent times is magnetic resonance imaging (MRI), which is performed with hyperpolarized gases such as helium (^{3}He) or Xenon (^{129}Xe) and allows the evaluation of anatomy and lung function with greater sensitivity than spirometry, lacking the ionizing radiation of computed tomography [11]. In asthma, ^{3}He MRI or ^{129}Xe MRI allows direct visualization of how the gas is distributed, identifying inhomogeneity and ventilation defects (poorly ventilated or non-ventilated areas) in real time with high spatial resolution [12]. In addition, MRI with hyperpolarized gases can measure smooth muscle dysfunction, inflammation, remodeling, airway lumen occlusions, alveolar microstructure, and gas exchange [13]. Figure 3 shows the schematic representation of a normal lung and one with regional ventilation alterations. However, lung MRI may have some limitations in young children, such as artifacts produced by involuntary movements of the heart, lung, or digestive system. Due to the extended length of the examination, many children may require sedation or anesthesia to remain still and reduce motion artifacts [14]. Other limitations include the high cost of the exam, its limited availability, and lower sensitivity compared to other radiological methods (for example, computed tomography) in detecting small pulmonary nodules, calcifications, cysts, bronchiectasis, or air trapping [15].

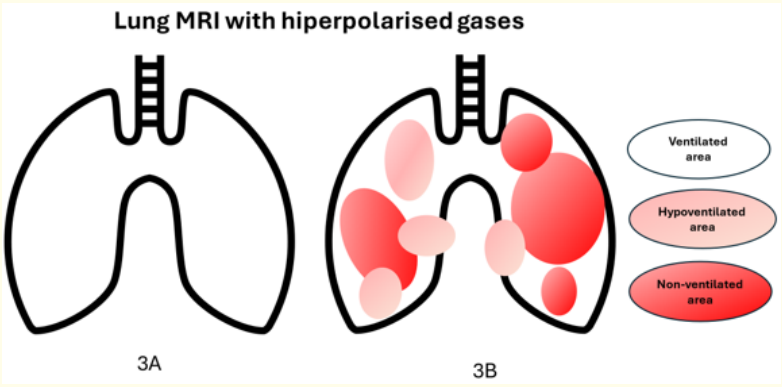

Figure 3: *Schematic representation of the lung image in an MRI with hyperpolarized gases. 3A: Normal lung, 3B: Lung with inhomogeneity and regional ventilation defects.*

Inhomogeneity and risk of asthma

A study showed that 19% of infants with recurrent wheezing had LCI values above the upper limit of normal (z-score > 1.64), an index that was significantly correlated with the fractional exhaled nitric oxide ($rs = 0.61$, $p = 0.004$). Furthermore, in this study, infants with recurrent wheezing had a 0.84-point higher LCI z-score ($p < 0.001$) than healthy controls [16]. In preschoolers aged 4 to 6 years with recurrent wheezing due to multiple triggers, significantly higher levels of LCI were found than in infants with wheezing caused only by viruses and healthy controls [17]. The LCI performed on 3-year-old preschoolers presenting with frequent respiratory symptoms has been shown to have a high ability to discriminate (AUC = 0.85) between children who continue or do not continue to have persistent wheezing at the age of 5 years [18]. In children under 24 months of age with a history of hospitalization for moderate to severe bronchiolitis, it has been shown that those caused by rhinovirus had significantly higher LCI ($p = 0.04$) and greater alterations in the inhomogeneity in the conduction pathways ($p = 0.01$) at preschool age, than those in whom bronchiolitis was due to another germ [19]. It has also been shown that preschoolers with a medical diagnosis of asthma have more alterations in the homogeneity of conductive ventilation ($p = 0.007$) than healthy controls; in this study, these alterations had a moderate power to discriminate (AUC = 0.7) between asthmatics and healthy subjects [20]. In the follow-up of preschool children with a history of recurrent wheezing and at least one exacerbation in the last year, it has been shown that they persistently bear elevated LCI values despite being classified as controlled according to asthma symptom control surveys [21]. In schoolchildren and adolescents with clinically stable asthma of different degrees of severity, significantly higher LCI

values have been found than in healthy controls, even with normal forced expiratory volume in the first second [22-25]. Small airway VI has also been correlated with inflammatory markers such as FeNO and bronchial hyperresponsiveness in schoolchildren and adolescents with asthma [26,27]. Further, a recent study has shown that preschoolers with respiratory symptoms and bronchial hyperreactivity may persist with small airway abnormalities and ventilation inhomogeneity into school age [28].

Inhomogeneity and severity of asthma

In children and adolescents with asthma, the LCI, Sacin, and Scond were shown to have a moderate level of accuracy (AUC = 0.76, 0.73, and 0.71, respectively) in differentiating between uncontrolled and controlled asthmatics [29]. It has also been shown that asthmatic children and adolescents with recent exacerbations or poorly controlled symptoms have significantly higher averages of LCI, Sacin and Scond ($p< 0.05$), than those with stable asthma [30]. Children and adolescents with severe asthma have been shown to have significantly higher LCI and more VI than mild to moderate asthmatics or healthy controls, despite improvement in other clinical and lung function variables with treatment [31,32]. Children and adolescents with severe therapy-resistant asthma (STRA) have significantly higher LCI than those with difficult asthma and healthy controls. In addition, 65% of children with STRA treated with systemic corticosteroids (triamcinolone) normalize their LCI in accordance with FeNO, suggesting that they may correspond to an eosinophilic phenotype with poor response to inhaled corticosteroids [33].

Hyperpolarized ^{3}He MRI has shown that children with severe asthma have higher percentages of ventilation defects than children with less severe asthma. In this study, the percentage of ventilation defects was significantly correlated with higher use of inhaled corticosteroids, higher treatment needs, and higher total eosinophil counts, and negatively correlated with asthma control scores or lung function parameters [34]. Another investigation, conducted in children and adolescents, demonstrated that ventilation defects and the number of ventilation defects per image slice on a ^{129}Xe MRI were correlated with asthma severity and have the adequate capability to predict patients requiring further medical attention or oral corticosteroid use [35]. Children with poorly controlled asthma who had higher ventilatory heterogeneity indexes on ^{3}He MRI, had significantly higher percentages of airflow limitation, greater bronchodilator response on spirometry, higher blood eosinophil counts, nitric oxide levels, and eosinophilic/neutrophilic pattern on bronchoalveolar lavage, than those with less ventilatory heterogeneity [36]. Lastly, in well-controlled children with severe asthma undergoing ^{129}Xe MRI, a decrease in post-bronchodilator ventilation defects was found, but not in LCI, which could indicate persistent small airway inhomogeneity [37].

Conclusion

VI could be considered a useful physiological parameter to discriminate between children with recurrent wheezing or asthma and healthy individuals at a young age. The LCI is also useful in the monitoring of pediatric asthma, as it allows for the detection of altered ventilatory homogeneity that persists after treatment in patients who report the absence of asthma symptoms or have normal spirometry. Children and adolescents with severe asthma have significantly higher rates of inhomogeneity measured by the LCI, Scond, Sacin indices, or MRI with hyperpolarized gases than milder asthmatics and healthy controls. In this group of patients, inhomogeneity is associated with a greater need for treatment, worse lung function, a greater bronchodilator response, and a higher degree of allergic inflammation. Therefore, it could be a useful pathophysiological parameter for monitoring severe asthma. Nonetheless, the functionality of these methods in pediatric asthma is still limited, restricted to specialized centers and studies with low patient numbers, meaning further development of future research in this field is required.

Bibliography

1. Gibson PG., *et al*. "Ventilation heterogeneity is a treatable trait in severe asthma". *Journal of Allergy and Clinical Immunology: In Practice* 12.4 (2024): 929-935.e4.

2. Sandra Rutting., *et al*. "Lung heterogeneity as a predictor for disease severity and response to therapy". *Current Opinion in Physiology* 22 (2021): 100446.

3. Foo CT., *et al*. "Assessment of ventilation heterogeneity in severe asthma using phase-resolved functional lung magnetic resonance imaging". *Physiological Reports* 13.12 (2025): e70423.

4. Alamoudi A., *et al*. "Effects of biologic therapy on novel indices of lung inhomogeneity in patients with severe type-2 high asthma". *BMJ Open Respiratory Research* 12.1 (2025): e002721.

5. Ramsey KA., *et al*. "Global Lung Function Initiative reference values for multiple breath washout indices". *European Respiratory Journal* 64.6 (2024): 2400524.

6. Bhakta NR., *et al*. "European Respiratory Society/American Thoracic Society technical statement: standardisation of the measurement of lung volumes, 2023 update". *European Respiratory Journal* 62.4 (2023): 2201519.

7. Stanojevic S., *et al*. "Multiple breath washout: measuring early manifestations of lung pathology". *Breathe (Sheff)* 17.3 (2021): 210016.

8. Robinson PD., *et al*. "ATS assembly on pediatrics. preschool multiple-breath washout testing. an official american thoracic society technical statement". *American Journal of Respiratory and Critical Care Medicine* 197.5 (2018): e1-e19.

9. Nuttall AGL., *et al*. "Lung clearance index: assessment and utility in children with asthma". *European Respiratory Review* 28.154 (2019): 190046.

10. Riley M., *et al*. "Looking beyond LCI: Multiple breath washout phase III slope derived indices and their application in chronic respiratory disease in children". *Pediatric Pulmonology* 59.12 (2024): 3085-3094.

11. Matheson AM., *et al*. "New frontiers in asthma chest imaging". *Journal of Allergy and Clinical Immunology* 155.2 (2025): 241-254.e1.

12. Kooner HK., *et al*. "Pulmonary functional MRI: Detecting the structure-function pathologies that drive asthma symptoms and quality of life". *Respirology* 27.2 (2022): 114-133.

13. Stewart NJ., *et al*. "Lung MRI with hyperpolarised gases: current and future clinical perspectives". *British Journal of Radiology* 95.1132 (2022): 20210207.

14. Serai SD., *et al*. "Pediatric lung MRI: Currently available and emerging techniques". *American Journal of Roentgenology* 216.3 (2021): 781-790.

15. Sodhi KS. "Lung MRI in children: the road less travelled". *Indian Journal of Radiology and Imaging* 31.1 (2021): 237-241.

16. Lu Z., *et al*. "Ventilation inhomogeneity in infants with recurrent wheezing". *Thorax* 73.10 (2018): 936-941.

17. Sonnappa S., *et al*. "Symptom-pattern phenotype and pulmonary function in preschool wheezers". *Journal of Allergy and Clinical Immunology* 126.3 (2010): 519-26.e1-7.

18. Safavi S., *et al*. "Lung clearance index predicts persistence of preschool wheeze". *Pediatric Allergy and Immunology* 33.1 (2022): e13713.

19. Sena CRDS., *et al*. "Bronchiolitis hospital admission in infancy is associated with later preschool ventilation inhomogeneity". *Pediatric Pulmonology* 59.3 (2024): 632-641.

20. Vilmann L., *et al*. "Fractional exhaled nitric oxide and multiple breath nitrogen washout in preschool healthy and asthmatic children". *Respiratory Medicine* 133 (2017): 42-47.

21. Kowalik K., *et al*. "Persistent ventilation inhomogeneity after an acute exacerbation in preschool children with recurrent wheezing". *Pediatric Allergy and Immunology* 31.6 (2020): 608-615.

22. Zwitserloot A., *et al*. "Clinical application of inert gas Multiple Breath Washout in children and adolescents with asthma". *Respiratory Medicine* 108.9 (2014): 1254-1259.

23. Racette C., *et al*. "Lung clearance index is elevated in young children with symptom-controlled asthma". *Health Science Reports* 1.8 (2018): e58.

24. Macleod KA., *et al*. "Ventilation heterogeneity in children with well controlled asthma with normal spirometry indicates residual airways disease". *Thorax* 64.1 (2009): 33-37.

25. Singer F., *et al*. "Abnormal small airways function in children with mild asthma". *Chest* 145.3 (2014): 492-499.

26. Keen C., *et al*. "Small airway function, exhaled NO and airway hyper-responsiveness in paediatric asthma". *Respiratory Medicine* 105.10 (2011): 1476-1484.

27. Steinbacher M., *et al*. "Small airway function before and after cold dry air challenge in pediatric asthma patients during remission". *Pediatric Pulmonology* 52.7 (2017): 873-879.

28. Määttä AM., *et al*. "Early childhood lower-airway symptoms and airway hyperresponsiveness linked to school-age small-airway dysfunction". *Journal of Allergy and Clinical Immunology: Global* 4.2 (2025): 100454.

29. Wawszczak M., *et al*. "Diagnostic accuracy of peripheral lung function measurements in paediatric asthma control assessment: a pilot study". *Postępy Dermatologii i Alergologii* 40.6 (2023): 772-778.

30. Wawszczak M., *et al*. "Peripheral airways involvement in children with asthma exacerbation". *Clinical Respiratory Journal* 16.2 (2022): 97-104.

31. de Gouveia Belinelo P., *et al*. "Clinical and lung function outcomes in a cohort of children with severe asthma". *BMC Pulmonary Medicine* 20.1 (2020): 66.

32. Nuttall AG., *et al*. "Ventilation heterogeneity in children with severe asthma". *European Journal of Pediatrics* 180.11 (2021): 3399-3404.

33. Irving S., *et al*. "Lung clearance index and steroid response in pediatric severe asthma". *Pediatric Pulmonology* 55.4 (2020): 890-898.

34. Altes TA., *et al*. "Clinical correlates of lung ventilation defects in asthmatic children". *Journal of Allergy and Clinical Immunology* 137.3 (2016): 789-96.e7.

35. Lin NY., *et al*. "129Xe MRI as a measure of clinical disease severity for pediatric asthma". *Journal of Allergy and Clinical Immunology* 147.6 (2021): 2146-2153.e1.

36. Gerald Teague W., *et al*. "Measures of ventilation heterogeneity mapped with hyperpolarized helium-3 MRI demonstrate a T2-high phenotype in asthma". *Pediatric Pulmonology* 56.6 (2021): 1440-1448.

37. Safavi S., *et al*. "Evaluating post-bronchodilator response in well-controlled paediatric severe asthma using hyperpolarised 129Xe-MRI: A pilot study". *Respiratory Medicine* 180 (2021): 106368.

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