



Editorial

Small Airway Disease in Asthma: Why is it so Important?



In the last fifty years, the role of small airways in chronic obstructive pulmonary disease has been thoroughly investigated owing to the availability of novel tools¹ and technologies² to assess different aspects of the multifaceted peripheral respiratory compartment once called “the lung silent zone”.³ Small airways with a diameter less than 2 mm are a bridge between the central airways and the gas-exchange lung compartment. Under normal conditions, the contribution of small airways to the total airway resistance is modest.⁴ However, there is both direct and indirect evidence indicating that the contribution of this anatomical zone to the overall airway resistance, among others, becomes prominent in obstructive lung diseases, including asthma.⁵ Pathology has confirmed the presence of small airway abnormalities in asthma, irrespective of the degree of severity, from mild to moderate to very severe asthma.^{6,7} There are three key concepts to understanding the relevance of small airway dysfunction (SAD) in asthma: is SAD frequent in asthma? Is it related to the clinical outcomes and is it specific to any phenotype?

Is SAD frequent in asthma?

In the last few decades, several methods have been developed to assess SAD; however, there is no single gold standard measurement. Indeed, each tool provides different information in the description/pathophysiology of SAD, from peripheral airway resistance, reactance, air trapping, heterogeneity of peripheral ventilation to imaging of the lung periphery.⁸ The studies conducted in this field consistently showed, by different techniques, the high prevalence of SAD across the entire spectrum asthma severity. The Assessment of Small Airways Involvement in Asthma (ATLANTIS) study recently specifically evaluated small airway impairment in patients with asthma by using all the available methods to assess SAD with different disease severities.⁹ This large multicentre study showed that small airway abnormalities can be identified by at least one of the tests in up to 90% of cases. This suggests that virtually all patients with asthma have small airway impairment.

Is SAD related to clinical outcomes in asthma?

From a clinical perspective, it is relevant to understand not only whether SAD is frequent, but more importantly, whether SAD affects clinical outcomes in asthma. SAD has been associated with important asthma clinical outcomes, such as dyspnoea,¹⁰ particularly in nocturnal asthma^{11,12} and exacerbations.¹³ Interestingly, several studies have shown that impairment in small airways, even

in patients with normal lung function, is associated with a lack of asthma control. Such an association has been shown by means of functional parameters related to SAD, including impulse oscillometry and nitrogen washout test,¹⁴ as well as measurements of peripheral airway inflammation such as alveolar NO.¹⁵ These data clearly indicate a correlation between (low) asthma control and small airway impairment, even when FEV₁ is still within the normal range. Additional analysis from the ATLANTIS study documented (as presented so far as scientific communications at international congresses) that the measurement of SAD in asthma is prospectively associated with the future risk of exacerbations.¹⁶ The Atlantis study, by assessing SAD with different tools, showed that the greater the impairment of small airways, the greater the severity of the clinical condition in terms of asthma control, exacerbation frequency and severity, quality of life, and treatment intensity.⁹ A composite score of SAD (ordinal score) obtained by IOS parameters predicted asthma exacerbations and asthma control, confirming, in a prospective fashion, the association between the dysfunction of small airways and these clinical outcomes.¹⁷ Notably, in a multivariate analysis, FEV₁ was no longer a significant predictor of exacerbations when the ordinal score was included in the model.¹⁷ An overview of these relations are summarized in Table 1.

Is SAD specific for some phenotypes of asthma?

Phenotyping can allow personalized management and treatment. As such, the term “Trait” has been recently introduced, with “Treatable trait” indicating a clinical/marker characteristic for which a treatment is available. In severe asthma, some phenotypes with a poor response to treatment have documented small airway impairment. Findings from the Severe Asthma Research Network (SARP) showed that patients with severe asthma have prominent air trapping, detected as increased an RV/TLC ratio, rather than airflow obstruction defined as the FEV₁/FVC ratio.¹⁸ When the trait “duration of the disease” was considered, higher lung function indices of air trapping correlated with small airway impairment in older asthma patients.¹⁹ A progressive and significant increase in residual volume over a 5 year follow up has been shown in asthmatic patients with a trait of fixed airflow obstruction compared with fully reversible airflow obstruction.²⁰ Finally, smoking habits have deleterious effects and negative impacts on human health. In asthma, this trait reduces corticosteroid responsiveness, accelerates lung function decline, and increases the risk of poor dis-

Table 1
Small airways disease impairment and clinical outcomes.^{9,14,17}

	Modest small airway Impairment	Relevant small airway Impairment
Asthma treatment steps		
GINA 1–2,	+	+/-
GINA 3,	+	+
GINA 4–5	+	+++
Duration of disease	–	Longer
Exacerbation risk (prior and future)	↑ ↑ ↑ Increases with impairment severity (17)	
Severe exacerbations	–	More frequent
Asthma control	–	Worse
Health status	–	Worse

ease control.²¹ Notably, cigarette smoking aggravates small airway abnormalities in patients with asthma.²²

For all these reasons, we believe that evaluation of small airways is clinically important in the overall assessment of patients with asthma and that small airways are relevant targets for inhaled treatments. The small particle size of inhaled drugs has been shown to improve the deposition of delivered treatments throughout the entire bronchial tree, particularly in the peripheral compartment.²³ Randomized control trials have shown that similar functional outcomes can be achieved with approximately half the dose of extrafine formulation as with non-extrafine formulations.^{24,25}

Conclusions

Given the relevance of small airways in the clinical outcome of asthma, the identification, by whatever means, of SAD could provide relevant information to optimize/personalize the management of asthma patients. Limiting the functional/inflammatory assessment of large airways (mainly FEV1) could preclude the identification of dysfunctions of the respiratory system that can be present very early in the evolution of the disease.

Conflict of interests

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References

- Contoli M, Bousquet J, Fabbri LM, Magnussen H, Rabe KF, Siafakas NM, et al. The small airways and distal lung compartment in asthma and COPD: a time for reappraisal. *Allergy*. 2010;65:141–51.
- Ueda T, Niimi A, Matsumoto H, Takemura M, Hirai T, Yamaguchi M, et al. Role of small airways in asthma: investigation using high-resolution computed tomography. *J Allergy Clin Immunol*. 2006;118:1019–25.
- Mead J. The Lung’s quiet zone. *N Engl J Med*. 1970;282:1318–9.
- Macklem PT, Mead J. Resistance of central and peripheral airways measured by a retrograde catheter. *J Appl Physiol*. 1967;22:395–401.
- Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. *Am Rev Respir Dis*. 1990;141:584–8.
- Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, et al. Inflammation of small airways in asthma. *J Allergy Clin Immunol*. 1997;100:44–51.
- Mauad T, Silva LFF, Santos MA, Grinberg L, Bernardi FDC, Martins MA, et al. Abnormal alveolar attachments with decreased elastic fiber content in distal lung in fatal asthma. *Am J Respir Crit Care Med*. 2004;170:857–62.
- Scichilone N, Contoli M, Paleari D, Pirina P, Rossi A, Sanguinetti CM, et al. Assessing and accessing the small airways; implications for asthma management. *Pulm Pharmacol Ther*. 2013;26:172–9.
- 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 Respir Med*. 2019.

10. Takeda T, Oga T, Niimi A, Matsumoto H, Ito I, Yamaguchi M, et al. Relationship between small airway function and health status, dyspnea and disease control in asthma. *Respiration*. 2010;80:120–6.
11. Kraft M, Pak J, Martin RJ, Kaminsky D, Irvin CG. Distal lung dysfunction at night in nocturnal asthma. *Am J Respir Crit Care Med*. 2001;163:1551–6.
12. Abdo M, Trinkmann F, Kirsten A-M, Biller H, Pedersen F, Waschki B, et al. The relevance of small airway dysfunction in asthma with nocturnal symptoms. *J Asthma Allergy*. 2021;14:897–905.
13. in't Veen JC, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. *Am J Respir Crit Care Med*. 2000;161:1902–6.
14. Bourdin A, Paganin F, Préfaut C, Kieseler D, Godard P, Chanez P. Nitrogen washout slope in poorly controlled asthma. *Allergy*. 2006;61:85–9.
15. Scichilone N, Battaglia S, Taormina S, Modica V, Pozzecco E, Bellia V. Alveolar nitric oxide and asthma control in mild untreated asthma. *J Allergy Clin Immunol*. 2013;131:1513–7.
16. Kraft M, Nicolini G, Berge MVD, Brightling C, Fabbri L, Molen TVD, et al. Small Airways Dysfunction (SAD) correlates with relevant asthma outcomes: longitudinal results from the Assessment of small Airways involvement in asthma (ATLANTIS) Study. *Eur Resp J*. 2020;58 Suppl. 65:PA3722.
17. Kraft M, Richardson M, Hallmark B, Billheimer D, Van Den Berge M, Fabbri LM, et al. Small airways dysfunction predicts asthma control and exacerbations: Longitudinal Data from ATLANTIS Study. *Eur Resp J*. 2021;56 Suppl. 64:139.
18. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007;119:405–13.
19. Cassino C, Berger KI, Goldring RM, Norman RG, Kammerman S, Ciotoli C, et al. Duration of asthma and physiologic outcomes in elderly nonsmokers. *Am J Respir Crit Care Med*. 2000;162:1423–8.
20. Contoli M, Baraldo S, Marku B, Casolari P, Marwick JA, Turato G, et al. Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. *J Allergy Clin Immunol*. 2010;125:830–7.
21. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J*. 2012;41:716–26.
22. Contoli M, Bellini F, Morandi L, Forini G, Bianchi S, Gnesini G, et al. Assessing small airway impairment in mild-to-moderate smoking asthmatic patients. *Eur Respir J*. 2016;47:1264–7.
23. Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. *Lancet Respir* 2014;2:497–506.
24. Papi A, Paggiaro PL, Nicolini G, Vignola AM, Fabbri LM, group on behalf of the ICAT versus symbicort (ICAT SY) study. Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma. *Eur Respir J*. 2007;29:682–9.
25. Papi A, Paggiaro P, Nicolini G, Vignola AM, Fabbri LM. Beclomethasone/formoterol vs fluticasone/salmeterol inhaled combination in moderate to severe asthma. *Allergy*. 2007;62:1182–8.

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