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Small Airways Disease and Asthma Management: Is there a Connection?

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ABSTRACT

We reviewed literature on the assessment and prevalence of small airways impairment in asthma and the relationships between small airways disease (SAD) and asthma clinical characteristics. The effects of treatments targeting small airways alterations are also discussed. We performed a PubMed search, using "asthma AND small airways" and "small airways AND treatment". All identified works were reviewed for adequacy, including reviews, randomised clinical trials and real-life studies. We found evidence that SAD is highly prevalent in the asthma population, throughout all degrees of severity. SAD seems particularly pronounced in some specific phenotypes and in severe asthma. Further studies are needed to investigate the mechanisms of the association between SAD and clinical outcomes such as symptom control and exacerbation risk. The inhaled treatment with recently developed small particle size formulations warrants a greater drug deposition in the more peripheral district and positively affects clinical outcomes while reducing the overall drug exposure. **(BRN Rev. 2018;4:16-33)**

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INTRODUCTION

Asthma is a common condition, usually characterised by chronic inflammation of the airways[1]. It is a clinically heterogeneous disease, involving many elements in determining the variability that characterises the clinical presentation of the disease. In past years, many efforts were made to identify clusters of patients who share common demographic, clinical and/or pathophysiological characteristics, which have been termed asthma phenotypes[2,3]. In this context, several investigators have questioned the relevance of pathophysiological changes in the more peripheral divisions of the airways and whether they are associated with specific clinical presentation and/or susceptibility to treatment. Indeed, despite being considered for a long time a disease primarily affecting central airways, it is now well documented that profound rearrangements occur in the distal areas of the airways of asthmatic patients[1].

Small airways were defined in the 1970s as the partition of airways with a diameter < 2 mm, without cartilage in their walls and originating from the eighth bronchial division down to the respiratory bronchioles[4]. In past years, they have been termed the silent zone of the lung, in relation to the difficulty of evaluation with conventional methods and to the supposed relatively low contribution to total airway resistance[5]. In recent years, the pathophysiology of small airways and of their role in clinical outcomes of asthma has been more systematically addressed with the development of diagnostic tools investigating the peripheral district from different viewpoints.

ASSESSING SMALL AIRWAYS DISEASE IN ASTHMA: OVERVIEW AND PREVALENCE

The analytical description of the instruments that have been used to investigate small airways in asthma has been the specific objective of recent reviews to which we refer for additional details.

Bronchioles, terminal bronchioles and alveolar ducts/sacs are the main structures considered as small airways (Fig. 1). They are characterized by diameter < 2 mm, a large cross-sectional area of about 140 m^2 and a volume of approximately 4,500 ml that accounts for 98.8% of the total lung volume[6]. In asthma with small airways disease (SAD), an increase in airway smooth muscle mass, mucus plugging, and goblet cell hyperplasia is present in the most peripheral part of the lung with an inflammatory cellular profile mainly characterized by infiltration of mast cells, eosinophils and CD4 Th2 lymphocytes[7,8].

The pathology of small airways in asthma has been mainly assessed in surgical/autoptic specimens or transbronchial biopsies[9]. These studies showed increased inflammation and substantial rearrangement of peripheral airways with altered composition of bronchiolar walls and of alveolar attachments with reduction in elastic fibre content. However, most of these data refer to severe asthma or asthma deaths, and limited information is available in mild asthma conditions[8,10-12].

The pathophysiology of SAD has been studied via invasive endobronchial catheterisation

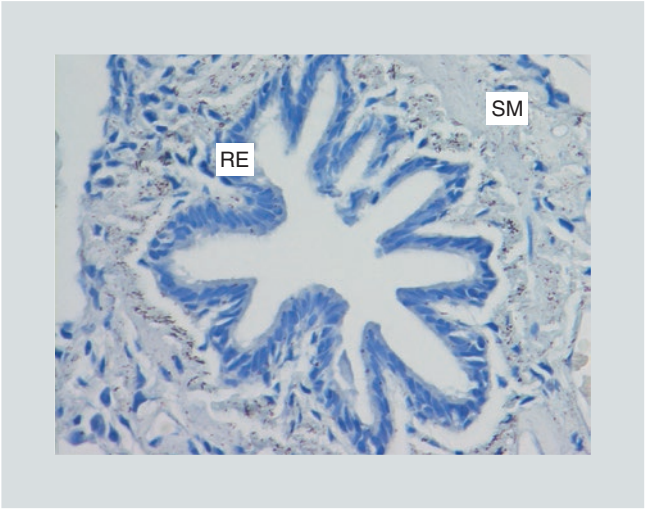

FIGURE 1. Section highlighting small airways.
RE: respiratory epithelium; SM: smooth muscle.

in asthmatic patients, documenting significantly increased resistance in the peripheral airways of asthmatic patients when compared to non-asthmatic controls, with higher resistance detected in patients with airflow obstruction[4,5,13,14].

Seminal physiology studies based on inert gas technique suggested that small airways impairment in asthma can lead to ventilation-perfusion inequality even in asymptomatic patients with normal spirometry[15,16]. In patients with ventilation-perfusion mismatch due to SAD, gas exchange might not deteriorate until forced expiratory volume in 1 second (FEV_1) reaches about 40% of predicted, and after that, gas exchange can rapidly worsen[17]. Spirometric data alone have therefore been suggested to have poor correlations with small airways alterations and may not clearly identify patients liable to serious gas exchange deterioration.

In recent years, several diagnostic tools have been developed to investigate small airways abnormalities noninvasively with different approaches, from lung function to imaging and to inflammatory markers, providing information on different aspects of small airways impairment (Table 1).

Spirometry and plethysmography can provide some indices related to SAD and the associated gas trapping and lung hyperinflation. Increased residual volume (RV), ratio between RV and total lung capacity (RV/TLC) and increased difference between slow and forced vital capacity (SVC–FVC), as well as decreased FVC, decreased forced expiratory flow at 25–75% ($FEF_{25-75\%}$) and 50% of forced vital capacity ($FEF_{50\%}$), have been considered as markers of small airways dysfunction. Their use is limited given their high physiological variability and because they are considered rough estimations of premature airway closure[18-24].

The single-breath nitrogen washout (SBN_2W) test can assess ventilation inhomogeneity and early closure of peripheral airways due to small airways dysfunction (phase III slope: dN_2, closing volume [CV], closing capacity [CC]) after a single inspiration of 100% oxygen from RV to TLC[25].

The multiple-breath nitrogen wash-out (MBN_2W) test is performed by the inhalation of 100% oxygen during tidal breathing[26]. It is a highly reproducible technique based on the rate and the extent of N_2 gas exhalation from the tracheobronchial tree, reflecting changes in lung ventilation in the whole lung, in proximal and conducting airways and in distal and acinar regions (Scond, Sacin)[27,28].

Forced oscillation technique (FOT) and impulse oscillometry (IOS) are effort-independent tests performed during tidal breathing that need

Table 1. Techniques used to assess small airways function

Test	Measures	Outcomes	Pros	Cons
Spirometry	FEF_{25-75}, FVC, SVC/FVC. (i.e. SVC minus FVC, see ref. 18)	Gas trapping, ventilation heterogeneity	Non-invasive, easy to perform, widely available, low costs	Influenced by central airways obstruction and volume changes, not very specific for SAD, poor reproducibility
Body plethysmography	TLC, FRC, RV, RV/TLC	Gas trapping, ventilation heterogeneity	Non-invasive, easy to perform, low variability, fair reproducibility	Further studies required
FOT/IOS	R5-R20, reactance at 5 Hz (X5), reactance area (AX)	Peripheral airways obstruction, resistance and capacitance	Non-invasive, easy to perform, fair reproducibility	Not widely available
MBN_2W	Sacin, Scond	Gas trapping, acinar and conductive ventilation heterogeneity	Non-invasive, good sensitivity, good reproducibility	Not widely available
SBN_2W	Closing volume, closing capacity, Phase III slope	Gas trapping, ventilation heterogeneity	Non-invasive, good sensitivity, good reproducibility	Not widely available
Exhaled NO	FeNO, CalvNO	Inflammation, remodelling of SAD	Non-invasive, fair reproducibility	Further studies required, time consuming, influenced by smoking, caffeine, diet
Late-phase sputum induction	Cell and cytokine profile	Airways inflammation	Non-invasive	High costs, little evidence, poor standardisation, unknown reproducibility
HRCT	Lung attenuation	Gas trapping, ventilation heterogeneity	Non-invasive, high resolution, good reproducibility	High costs, exposure to radiations
MRI	Lung attenuation	Gas trapping, ventilation heterogeneity	Non-invasive, high resolution, no radiations	Not widely available, complex, high costs
Bronchoscopy	Wedged airway resistance, transbronchial biopsy, BAL	Airway resistance, inflammation, remodelling	Direct assessment, highly informative	Invasive, time consuming, unknown reproducibility

AX: area of reactance; BAL: bronchial alveolar lavage; CalvNO: alveolar concentration of NO; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of forced vital capacity; FeNO: fractional exhaled nitric oxide; FOT/IOS: forced oscillation technique/impulse oscillometry; FRC: functional residual capacity; FVC: forced vital capacity; HRCT: high resolution computed tomography; MBN_2W: multiple breath nitrogen washout; NO: nitric oxide; R5: airways resistance at 5 Hz; MRI: magnetic resonance imaging; R20: airways resistance at 20 Hz; RV: residual volume; SAD: small airways disease; SBN_2W: single breath nitrogen washout; Scond, Sacin: multiple breath washout index of conductive and acinar ventilation heterogeneity; SVC: slow vital capacity; TLC: total lung capacity; X5: reactance at 5 Hz.

minimum patient cooperation[29,30]. In IOS small amplitude pressure oscillations are applied to the airways by a loudspeaker through a mouthpiece at different frequencies to measure airways impedance, resistance and reactance[31]. The difference between R5 (resistance at 5 Hz; total airway resistance) and R20 (resistance at 20 Hz; proximal airway resistance) indicates the resistance in the peripheral airways[32,33].

Imaging techniques by high-resolution computed tomography (HRCT) of the lungs can identify areas of different attenuation in the lung as a result of ventilation heterogeneity caused by SAD (Fig. 2)[34].

Magnetic resonance imaging (MRI) does not expose the patient to ionising radiation, but it has poor contrast resolution. The requirement of additional enhancement tools makes it difficult to use this technique in clinical practice[35,36].

To assess the inflammatory pattern of the more peripheral airways, sequential sputum induction

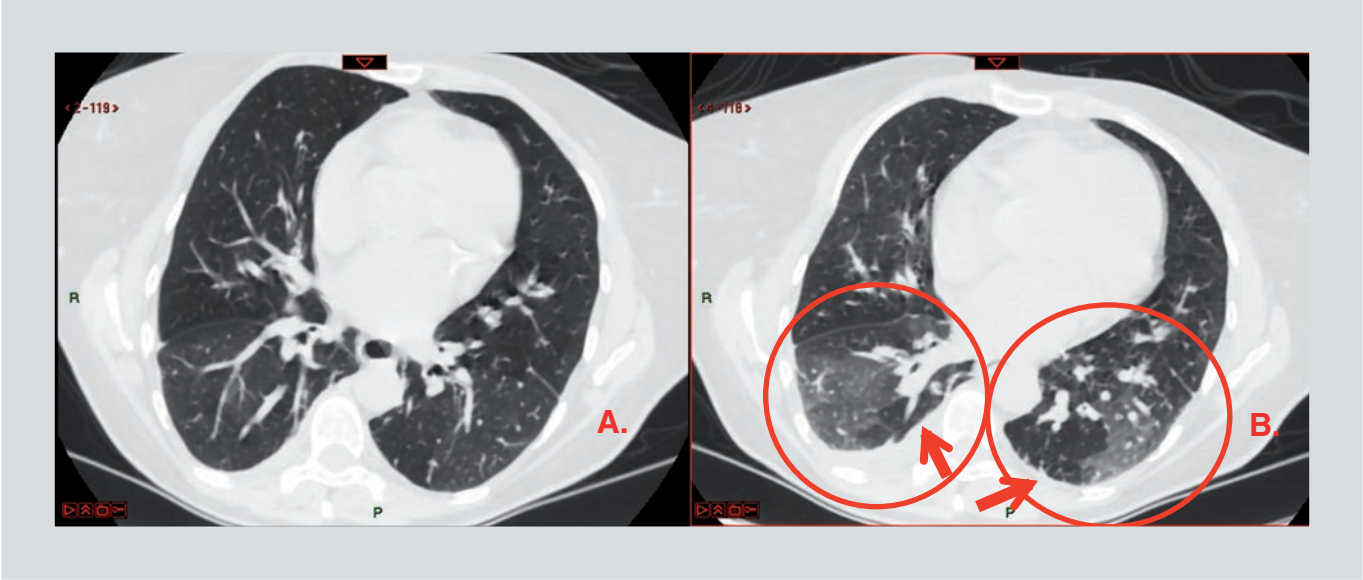

FIGURE 2. HRCT detection of gas trapping. **A)** Inspiratory CT sequence. **B)** Expiratory CT sequence (bronchodilators withheld by more than 12 hours) showing low lung attenuation areas (see arrows). CT: computed tomography; HRCT: high resolution computed tomography.

has been investigated, but the available techniques cannot reliably distinguish between different anatomical compartments[37,38].

Exhaled breath nitric oxide (eNO) is associated with airway inflammation[39]. By using different exhalation flow-rates, it is possible to distinguish NO produced in central airways (low exhalation flows) from NO generated in peripheral regions (high flows); back diffusion of NO is among the confounding factors of this latter type of assessment[40].

Recently, the prevalence of small airways dysfunction and alteration in asthma has been thoroughly reviewed for each individual modality of assessment. In table 2, we highlight some of the available data that are particularly informative.

Overall, SAD is present in the majority of the asthmatic population (between 50% and 60%), irrespective of the degree of severity, with a trend in increased prevalence with severity when imaging (HRCT) and lung function are the tools of assessment[52].

These data suggest that there is no unique technique or reference gold standard to identify the involvement of the small airways in the asthmatic population. The overall picture of SAD may then derive from the integration of different pieces of information obtained by different techniques (Fig. 3).

Pioneering analyses indicate that different parameters and techniques, when combined, can provide a more efficient instrument for the assessment of SAD[53].

However, the tools to detect small airways abnormalities and dysfunction are not always available in everyday clinical practice, and the assessment of SAD is not routinely performed. From a practical viewpoint, some

Table 2. Prevalence of SAD through different diagnostic techniques

Study	Patients	Tool of assessment	Measures	Prevalence of SAD
Manoharan et al.[41]	Unselected asthmatic patients (n = 442)	Spirometry	$FEF_{25–75}$	54%
Jain et al.[42]	Unselected asthmatic patients (n = 321)	Plethysmography	RV RV/TLC	52% 57%
Perez et al.[18]	Clinically stable moderate-to-severe asthmatic patients without proximal airways obstruction (normal FEV_1) (n = 222)	Spirometry, plethysmography	FRC, RV, RV/TLC	52%
	Clinically stable moderate-to-severe asthmatic patients with proximal airways obstruction (reduced FEV_1) (n = 219)	Spirometry, plethysmography	FRC, RV, RV/TLC	64%
Perez et al.[43]	Asthmatic patients with uncontrolled asthma (ACT < 20) (n = 324)	Spirometry, plethysmography	FRC RV	47% 49%
Alfieri et al.[44]	Mild to moderate asthma (n = 63)	Impulse oscillometry	R5–R20	48%
Anderson et al.[45]	Asthma patients BTS treatment stage 2 to 4 (n = 378)	Impulse oscillometry	R5–R20	BTS2 65% BTS3 64% BTS4 70%
Manoharan et al.[41]	Unselected asthmatic patients (n = 442)	Impulse oscillometry	R5–R20	42%
Pisi et al.[46]	Unselected asthmatic patients (n = 33)	Impulse oscillometry	R5–R20	33%
Gonem et al.[47]	Asthmatic patients GINA step 3 to 5	Multiple breath nitrogen washout	Sacin, Scond	46%
Hanon et al.[48]	Stable asthmatic patients (n = 66)	Multiple breath nitrogen washout	Sacin	53%
Verbanck et al.[49]	Stable asthmatic patients (n = 33)	Multiple breath nitrogen washout	Sacin	53%
Thompson et al.[50]	Exacerbated asthmatic patients (n = 18)	Multiple breath nitrogen washout	Sacin	61%
	Stable asthmatic controls (n = 19)			74%
Tunon-de-Lara et al.[51]	Uncontrolled mild-to-moderate asthmatics (n = 58)	HRCT	Gas trapping according to the definition of the Fleischner Society	56%

ACT: asthma control test; FEF 25–75%: forced expiratory flow at 25–75% of forced vital capacity; BTS: British Thoracic Society; FRC: functional residual capacity; HRCT: high resolution computed tomography; R5: airways resistance at 5 Hz; R20: airways resistance at 20 Hz; RV: residual volume; Sacin: indices of ventilation heterogeneity in the acinar; SAD: small airways disease; Scond: conductive; TLC: total lung capacity.

basic elements have been suggested to identify patients who deserve the assessment of the peripheral district most. These characteristics are summarised in table 3[52].

A large international study currently ongoing, the AssessmenT of smalL Airways involvemeNT In aSthma (ATLANTIS) study, was designed to assess small airways abnormalities by means of all known technologies currently available to investigate the peripheral district and identify clinical expression related to SAD in asthma. The study will also allow comparison and integration of the information obtained by capturing the different aspects of small airways alterations[54].

CLINICAL IMPACT OF SMALL AIRWAYS DISEASE IN ASTHMA: EVIDENCE AND LINKS

Asthma control and exacerbation risk reduction are the main goals of asthma management[1].

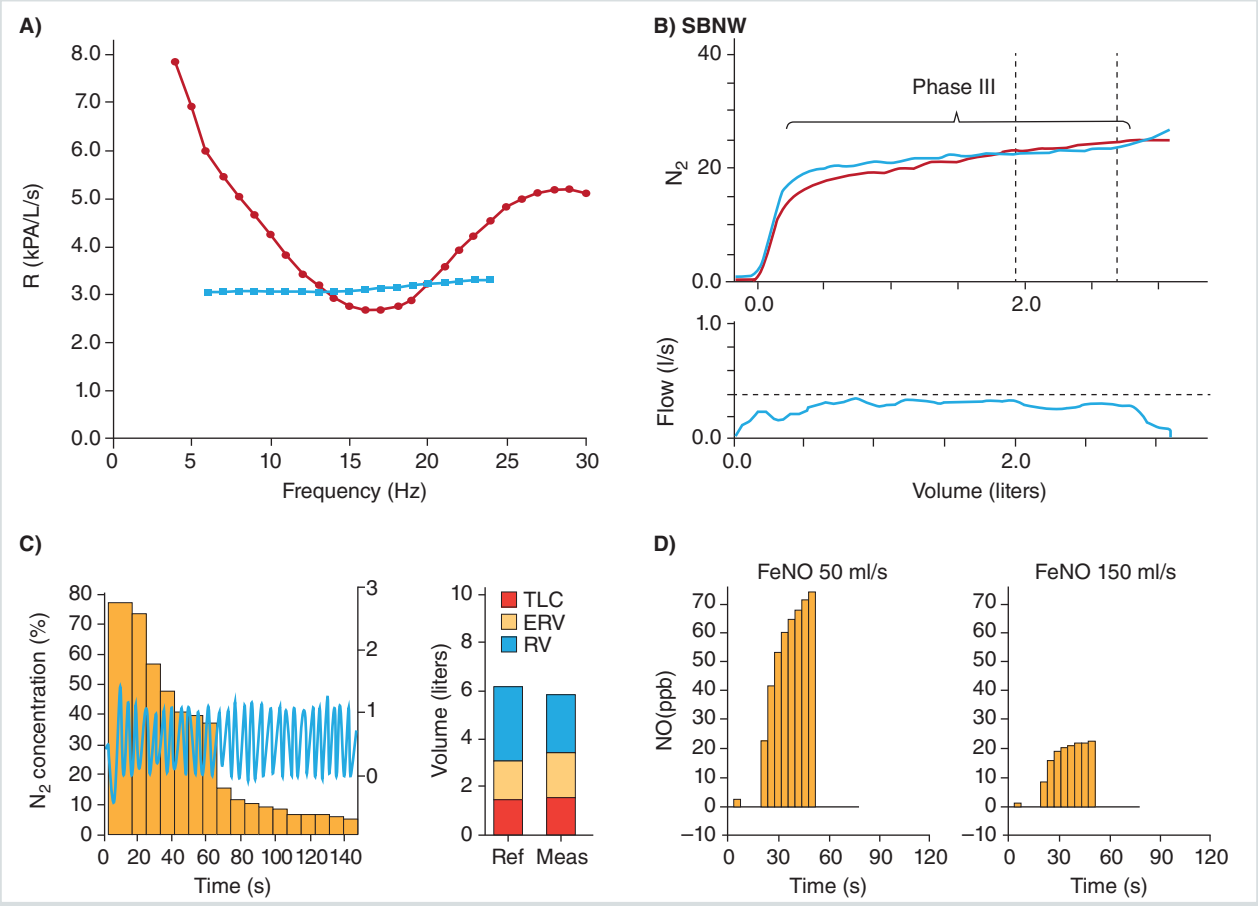

Figure 3. Examples of techniques for assessment of SAD. **A)** Example of graph obtained by IOS (in our centre in Ferrara) for the resistance study. On the X axis different frequencies of pressure oscillations emitted from the loudspeaker. On Y axes different airways resistance. **B)** Original example of graph obtained by single breath nitrogen washout (SBNW) test. On X axis lung volume. On Y axes level on N_2 during washout and air flow (the patient attempts to maintain a steady flow of air at 0.5 L/sec). Study of phase III slope is usually used as index of ventilation inhomogeneity. **C)** Original example of graphs obtained by multiple breath nitrogen washout (MBN_2W) test. The course of the N_2 washout can be used as a ventilation inhomogeneity index in small airways disease (SAD). On X axis time (s). On Y axis N_2 concentration and volume of patient tidal breathing (L). **D)** Original example of graphs obtained by fractional exhaled nitric oxide (FeNO). Levels of eNO at different flow rates can be considered as index of airways inflammation at different levels of the respiratory tree.
ERV: expiratory reserve volume; Meas: measured value, N_2: nitrogen; R: resistance; Ref: reference value: RV: residual volume; TLC: total lung capacity.

Table 3. Characteristics of the small airways asthma phenotype

Symptoms and clinic	– ACQ >1.5 – Persistent daytime and night-time symptoms
Therapy	– Regular use of reliever therapy in response to bronchoconstrictor stimuli or – A requirement for oral corticosteroids during a viral respiratory infection
Spirometric and functional features	– FEV_1 >80% – FEF 25%–75% <60%

ACQ: Asthma Control Questionnaire; FEF 25–75%: forced expiratory flow at 25–75% of forced vital capacity; FEV_1: forced expiratory volume in 1 second.

In real-world settings, asthma control is reported in less than 50% of the asthma population, a value substantially lower than that attainable in randomised controlled trials (RCTs)[55].

Among the causes of this gap, the inadequate treatment of SAD may contribute to maintaining an unstable inflammatory process and the pathophysiological mechanisms related to the clinical manifestation of the disease[56].

From a lung function perspective, FEV_1 is the parameter most frequently assessed in clinical practice (and in clinical trials), and yet its correlations with asthma symptoms are quite weak, suggesting that other components of the lung pathophysiology could contribute to the clinical expression of the disease and to asthma control[57].

From early pathology studies, it emerged that the peripheral district is affected by the same inflammatory process typically found in large airways in asthma. Bronchial alveolar lavage (BAL) fluid from asthmatic patients contains a higher number of eosinophils than that of healthy controls. Worse clinical scores have been associated with high eosinophils in BAL fluid, suggesting a correlation between involvement of the small airways and asthma clinical severity[58].

In a cohort of asthmatic children with documented airflow reversibility, it has been found that children with severe exacerbations had marked gas trapping, identified by increased RV and increased RV/TLC, compared to non-exacerbating children[59].

In addition, Takeda et al.[60], by spirometry and IOS assessments in asthmatic patients of different degrees of severity, found a weak correlation among FEV_1, health status and dyspnoea, whereas a significant association was found among peripheral airways (as assessed by IOS R5–R20) and health status and dyspnoea.

These data suggest that small airways can contribute, independently from large airways, to the clinical manifestations of asthma.

The involvement of small airways in specific clinical manifestations and outcomes of the disease has also been investigated. In adult asthmatics with preserved lung function, peripheral airways impairment (resulting in lower $FEF_{25–75}$ and lower R5–R20 values) significantly correlated with a higher risk of poor asthma control[61].

Similarly, the degree of asthma control (controlled versus uncontrolled) had been efficiently discriminated by IOS (R5–R20 and reactance area values) with a high sensitivity and specificity (84% and 86%, respectively) in asthmatic children[33].

On the same line, ventilation heterogeneity, assessed by MBN_2W or SBN_2W, has been repeatedly associated with poorly controlled asthma, suggesting that improvement in ventilation heterogeneity could lead to better symptom control[57].

It has also been reported that high alveolar heterogeneity, by SBN_2W testing, associates with both impaired asthma control and increased risk of exacerbations[62].

These data confirmed the relationship previously described between premature airway closure (air trapping (as assessed by means of SBN_2W) and the risk of exacerbation[63].

Thus, evidence is accumulating that small airways impairment is associated with reduced asthma control, increased exacerbations risk and worsening quality of life irrespective of the lung function measured by FEV_1[64].

What still needs to be clarified is the mechanism(s) by which the dysfunction of the peripheral district affects important asthma clinical outcomes. An interesting hypothesis involves alterations of the surfactant proteins.

Surfactant proteins, which are produced by type II alveolar epithelial cells, significantly contribute to lower superficial tension at the air-liquid surface of the distal airways, thus preventing them to collapse. They have also been linked to innate immune response in the distal airways, especially surfactant proteins A and D (SP-A, SP-D)[65,66]. Impaired production/function as consequence of inflammatory processes in the airways would lead to pathophysiological changes in peripheral airways, such as distal airways collapse and increased gas trapping[67]. Altered levels of surfactant proteins in BAL have been detected after specific airways challenge in asthmatic patients[68]. These data were confirmed in a recent study by Mackay et al.[69] who found decreased SP-D levels in BAL, but increased levels in serum, from severe asthmatic patients when compared to healthy controls. These authors suggested that higher serum SP-D levels could be due to increased vascular permeability to high molecular weight proteins as consequence of inflammatory process. Interestingly, higher serum surfactant protein D levels have been suggested as a marker of COPD severity of clinical usefulness[70]. Benfante et al.[71] investigated the relationship between surfactant D levels and asthma severity along with small airways impairment in 44 asthmatic patients, and found that higher serum levels of surfactant D significantly correlated to more severe disease (as defined by GINA treatment step) and with greater small airways impairment (as measured by IOS). These results, if confirmed in further studies, could broaden therapeutic approaches to asthma in the future.

At present, data from clinical trials with drug/inhaled formulation more effectively reaching the peripheral airways (discussed below) provide indirect evidence of the clinical consequences of improving the pathology and pathophysiology of peripheral airways.

SAD AND CLINICAL PHENOTYPES OF ASTHMA

Phenotypic characterisation is important to identify groups of patients who share common demographic, clinical and/or pathophysiological characteristics, have similar long-term outcomes and that can benefit from specific treatments to ameliorate the management of their disease[1].

Several studies in the past several years investigated whether the alterations of the peripheral district led to specific clinical phenotypic expression of the disease, such as nocturnal asthma, asthma in smokers, exercise-induced asthma, asthmatics with fixed airflow obstruction and severe or difficult-to-treat asthma[72].

The seminal studies in nocturnal asthma conducted on airway specimens obtained from

bronchial and transbronchial biopsies by Kraft et al.[11,73] showed that patients with nocturnal symptoms had a more relevant eosinophilic infiltration in the small airways than in the proximal airways, particularly in samples obtained during the night. This was associated with increased peripheral airways resistance assessed during bronchoscopy.

About 30% of the asthma population is actively exposed to cigarette smoking. These patients experience faster lung function decline[74], increased frequency of exacerbations[75], reduced asthma control[75,76] and a poor response to therapy with inhaled and systemic corticosteroids[77,78].

Tobacco smoking is known to have an impact on peripheral airways[79,80].

Indeed, in addition to the pathology/pathophysiology related to asthma, cigarette smoke promotes neutrophilic inflammation and airways remodelling in both central and peripheral airways[81,83].

By single-breath nitrogen washout test (SBNT), the phase III slope (dN_2) was found to be significantly higher in asthmatic smokers, indicating increased ventilation heterogeneity in the small airways of smokers with asthma. This has been confirmed by IOS showing increased small but not large airways resistance in smokers with mild-to-moderate asthma[84].

In mild and mild intermittent asthma, IOS performed after exercise testing showed greater impairment of small airways in patients with airways hyperresponsiveness (AHR) when compared with asthmatics without AHR, suggesting a role of small airways obstruction in the pathogenesis of exercise-induced bronchoconstriction[85].

Recent studies investigated the relationship between SAD and bronchial hyperresponsiveness. The results suggest that SAD, detected by different techniques is positively associated with BHR independently of FEV_1[86,87] and that SAD is associated with dyspnoea during such BHR testing[87].

The duration of the disease is one of the conditions reported to contribute to the development of asthma phenotype with fixed airflow limitation. It involves pathophysiological changes in the peripheral airways (degeneration of elastic fibres with loss of support to airways) increasing their collapsibility and premature closure, thus resulting in increased gas trapping[88-92].

Interestingly, there is a correlation between small airway abnormalities, as defined by air trapping (increased RV/TLC ratio), and duration of the disease that might be relevant in the development of the fixed airflow limitation asthma phenotype[93].

However, the exact relationship between SAD and fixed airflow obstruction is still debatable and requires *ad hoc* studies to be clarified.

It has been proposed to group all the clinical conditions above described under the term of "small airways phenotype" in recognition of the documented impairment of the peripheral district in these clinical conditions, as resumed in figure 4. This would include a group of patients whose clinical manifestations could be ascribed, at least in part, to a substantial impairment of the peripheral district and who would benefit most from treatments efficiently targeting peripheral airways[52,94].

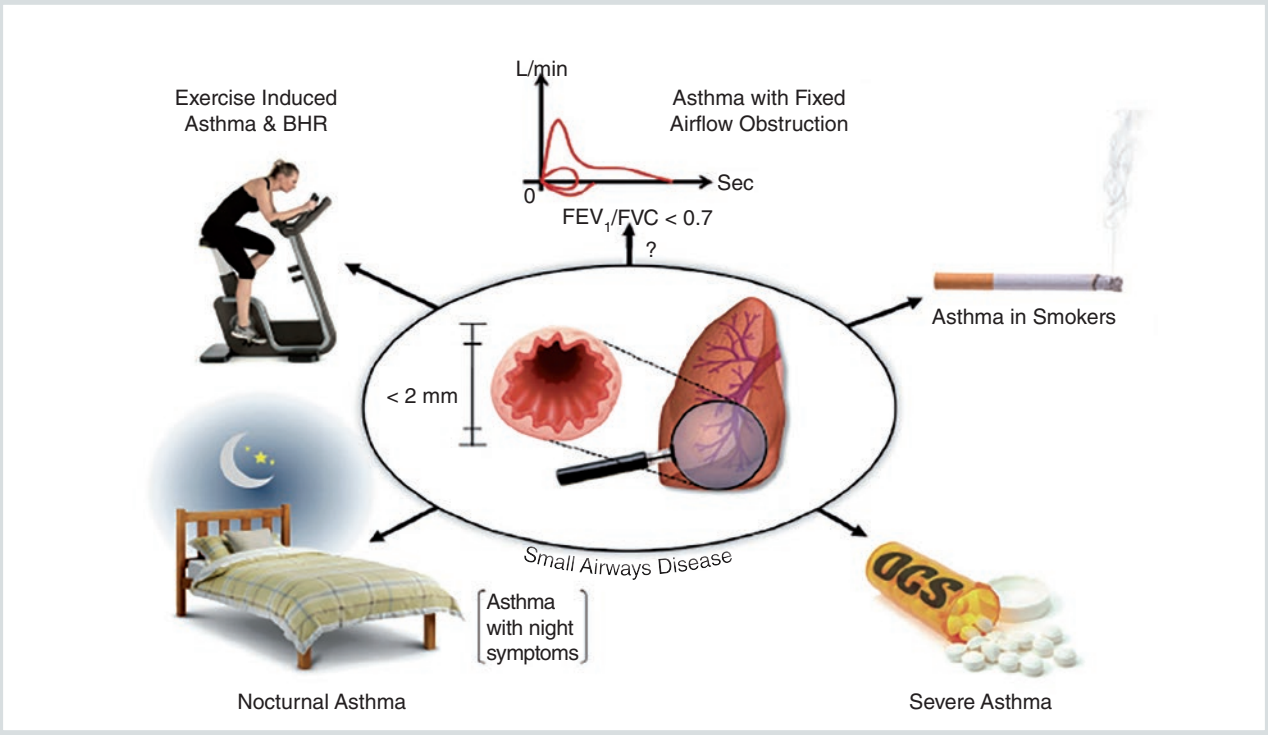

FIGURE 4. Small airways disease and asthma phenotypes.
BHR: bronchial hyperresposiveness; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; OCS: oral corticosteroids.

SAD IN SEVERE ASTHMA

Patients with severe asthma represent a minority (5 to 10%) of the asthmatic population, but they have a disproportionate impact on health care usage, contributing to the majority of the overall costs of asthma management[95].

Severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller and/or oral corticosteroids to prevent it from becoming uncontrolled, or that remains uncontrolled despite this treatment[96].

In recent years, several studies have been conducted to investigate the involvement and contribution of small airways in the pathogenesis of these severe clinical conditions. Overall, there is evidence of increased small airway dysfunction in severe versus mild to moderate asthmatic patients[97].

The enhanced small airway dysfunction could hamper the penetration and deposition of the inhaled treatments leaving undertreated, thus uncontrolled, the peripheral airways inflammation and its pathophysiological and clinical consequences.

Indeed, in specimens from patients who died from severe asthma exacerbation, massive inflammation and structural abnormalities of peripheral airways have been described[98-100].

An unanswered question remains, whether such alterations reflected the severity of the acute phase or whether they were related to the severity of the underlying disease.

Some indirect evaluations of inflammation in peripheral airways, assessed by alveolar NO, report higher values in refractory asthma compared to mild–moderate conditions, suggesting a more pronounced inflammatory process in the small airways of severe asthma[101], in line with available evidence in central airways[102].

Using IOS, the prevalence of SAD has been reported to be as high as 70% in severely asthmatic subjects[45].

The European Network for Understanding the Mechanisms of Severe Asthma (ENFUMOSA) Study network completed a multicentre prospective study comparing severe and mild asthmatic patients. By means of non-invasive techniques, reduced FVC and increased RV and RV/TLC ratios have been reported in severe asthma, indicating increased gas trapping and small airways dysfunction[103], in line with other studies of severe asthma[22].

Similarly, the Severe Asthma Research Programme (SARP) showed a significant reduction in FVC mean value in severe asthmatics when compared to mildly and moderately asthmatic patients[104].

Of particular interest are the results of a study by in't Veen et al.[63] in severe asthmatic patients, were frequent vs. infrequent exacerbators were compared. Using the SBN_2W test, they found increased CC and CV values in frequent exacerbators.

These data suggest the involvement of SAD in specific clinical expression of asthma severity, in particular a greater susceptibility to exacerbations.

The mechanisms that make severe-asthma patients with peripheral airways dysfunction more prone to exacerbations are unknown. It has been proposed that the peripheral partition of the airways is the most difficult to reach by inhalation therapy; thus, it remains relatively undertreated and more responsive to destabilising triggers.

It is likely that small airways dysfunction, although highly prevalent among severely asthmatic subjects, is not equally relevant in the pathophysiology of the different severe-asthma phenotypes.

ASTHMA TREATMENT: TARGETING SAD

Inhaled treatment is the preferred route of administration of asthma therapy[1].

In a seminal study, Usmani et al.[105], using lung scintigraphy, found that large particles (6 µm and 3 µm median mass aerodynamic diameter [MMAD]) have a greater deposition in proximal airways than smaller particles (1.5 µm), wich preferentially deposit in distal lung regions.

The smaller the size of inhaled particles, the greater is the penetration index. Small particle formulations provide lower oropharyngeal deposition that is related to both local and systemic side effects. Inhaled formulations with a high proportion of fine particle fraction (FPF), or respirable fraction (particles <5 microns in aerodynamic diameter) have greater lung deposition[106].

Iwanaga et al.[107] compared drug deposition of different inhaled treatments in the lungs, in mild to moderate persistent asthma, by using functional respiratory imaging, a computational fluid-dynamics–based CT elaboration. Inhaled treatment with high FPF resulted in greater lung deposition[107].

For environmental reasons, old chlorofluorocarbon (CFC) propellants have been banned and replaced by new hydrofluoroalkane (HFA) propellants. HFAs allowed the development of small particle size formulations. These formulations are available for ICS and fixed ICS/long-acting β_2 agonists (LABAs) combinations[23].

Their efficacy has been tested in both RCTs and in real-life studies, providing some evidence of the pathophysiological and clinical changes occurring when the peripheral district is more effectively targeted and drug deposition is higher in the peripheral airways.

I. PATHOPHYSIOLOGICAL AND CLINICAL OUTCOMES RELATED TO SMALL AIRWAYS: INHALED CORTICOSTEROIDS

Corticosteroid treatment represents the mainstay of asthma management. Several studies have assessed ICS small-particle/extra-fine formulations for pathophysiological and clinical outcomes.

Hauber et al.[108] investigated the effects of extra-fine HFA-beclomethasone dipropionate (BDP) versus large-particle dry powder inhaler (DPI)-budesonide on early- and late-phase sputum samples in patients with mild asthma. Although both treatments reduced sputum eosinophils and IL-4 and IL-5 mRNA expression in the early-phase sputum samples, only small-particle HFA-BDP reduced these markers in the late-phase samples that better reflect peripheral airway inflammation.

On lung function, ICS extra-fine formulation showed higher potency compared to a non-extra-fine formulation; Busse et al.[109] reported extra-fine BDP to be equipotent to a 2.6-times higher dose of CFC-BDP in improving FEV_1 and asthma control (daytime and night-time symptoms and use of reliever medication).

In the same line, by IOS, a greater reduction in peripheral airway resistance was found in asthmatic patients receiving HFA-BDP compared to a higher (double) CFC-BDP dose. Interestingly this difference was not observed on FEV_1[110].

In terms of quality of life, Juniper et al. showed greater improvement in the Asthma Quality of Life Questionnaire (AQLQ) in patients switched from CFC-BDP to half-dose extra-fine HFA-BDP, confirming the increased efficacy of these formulations, better reaching the small airways, on clinical outcomes[111].

Finally, imaging by HRCT confirmed the effects of extra-fine formulations on the peripheral district, showing a greater improvement in air trapping of extra-fine HFA-BDP compared to conventional CFC-BDP[112]. This provides a static picture of the peripheral changes induced by small particle formulations associated with lung function and clinical outcomes previously described.

Similar data on lung function (FEV_1) IOS, imaging, peripheral NO and asthma control

have been documented when extra-fine ciclesonide was investigated[113-115].

II. FIXED COMBINATION ICS/LABA: PATHOPHYSIOLOGICAL AND CLINICAL OUTCOMES RELATED TO SMALL AIRWAYS

In line with what previously has been described for ICSs, small particle ICS/LABA combinations positively affect small airways function and clinical outcomes.

Scichilone et al.[116], using an SBN_2W test, reported that the extra-fine BDP/Formoterol Fumarate (FF) combination improves both large and small airways function by reducing BHR and closing capacity than treatment with large particle ICS/LABA.

Interestingly, in a study conducted on patients with different degrees of asthma severity switched from previous treatment (either SABA, or ICS, ICS/LABA combinations) to extra-fine pMDI-BDP/formoterol, Vos et al.[117] observed significant improvements in lung function (FEV_1), airway inflammation (eNO), and gas trapping (HRCT) in association with benefits in clinical outcomes such as asthma control test (ACT score)[117].

ICS/LABA extra-fine formulations have been reported to be associated with an overall reduction in ICS dose and a good tolerability profile. Huchon et al.[118] assessed the clinical efficacy of extra-fine HFA-BDP/formoterol and of a 2.5 times higher dose of pMDI CFC-BDP non-extra-fine plus DPI formoterol. The study showed similar improvement in lung function by the two ICS/LABA combinations compared to high-dose BDP non-extra-fine and a higher level of asthma control and lower exacerbation risk with the extra-fine combination. In terms of safety, serum cortisol levels remained within the range of normality, given the lower doses of ICS that patients with extra-fine therapy were exposed to.

Small particle of ICS/LABA combinations have been tested in particular subgroups of asthmatic patients with small airways impairment. A recent study by Contoli et al.[84] reported that extra-fine BDP/formoterol (F) improves small airways–related parameters (dN2 measured by SBN_2W and R5–R20 measured by IOS) and the degree of asthma control in smoking asthmatic patients more effectively than in non-smoking asthmatic patients.

These studies highlight the importance of tailoring small-particle inhaled treatment in patients with more pronounced involvement in small airways.

III. SMALL PARTICLE FORMULATIONS AND REAL-LIFE STUDIES

At variance with RCT, real-life studies are closely associated with routine clinical practice. Indeed, they address clinical outcomes in an unselected asthma population and in clinical settings representing everyday clinical practice[119].

A meta-analysis recently completed reviewed the effectiveness of extra-fine ICS versus small-particle ICS (either alone or with in association with LABA) in real-life studies of asthma. The results indicate that the use of extra-fine formulation in real-life settings is associated with higher levels of asthma control, lower ex-

acerbation rates and lower exposure to ICS[120].

Müller et al.[121], comparing outpatients cross-sectionally with moderate to severe persistent asthma treated with fixed combinations of ICS/LABA, reported that the proportion of patients achieving asthma control was significantly higher in the extra-fine than in the non-extra-fine combinations. Notably, this was associated with a lower ICS mean daily dose.

An observational study conducted in the United Kingdom of asthmatic patients previously treated with large-particle ICS/LABA combinations that were prescribed extra-fine BDP/F showed a better level of asthma control and lower use of rescue medication with the latter treatment[122].

Their results were confirmed in other longitudinal studies showing improvement in health-related quality-of-life status with small-particle therapy[123,124].

In a real-life study, patients prescribed inhaled treatment with high respirable fraction particles showed improved clinical outcomes and low exacerbation rates[125].

A recent real-life study by Marth et al.[126] analysed the effects of treatment with extra-fine ICS/LABA in asthma patients considered more likely to have pronounced impairment of small airways (e.g., smoking asthmatics, patients with signs of gas trapping). The switch from previous treatment to extra-fine BDP/F treatment resulted in improved symptoms, reduced use of rescue medication and better asthma control and lung function (FEV_1, PEF and FVC) in the overall population and among subgroups of patients identified as having the small airway phenotype[126].

CONCLUSIONS

In the past several years, much interest has emerged in a relatively overlooked airways compartment: the small airways. SAD is very common among asthmatics, regardless of the severity of airflow obstruction and severity of the disease. SAD seems particularly pronounced in some specific phenotypes and in severe asthma. Data from pharmacological studies seem indirectly to support the hypothesis that therapies targeting the distal airways can positively influence asthma clinical outcome, particularly among patients with more pronounced small airways involvement. Many aspects however remain unclear, such as the mechanisms by which small airways impairment would affect clinical asthma features. In addition, most of the data have been obtained in small, single-centre studies. However, large real-life studies seem to support the conclusions obtained in strictly controlled conditions.

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CONFLICT OF INTEREST

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