



Review article

The prevalence of small airways disease in adult asthma: A systematic literature review

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ABSTRACT

Background: Small airways dysfunction and inflammation contribute significantly to the clinical impact of asthma, yet conventional methods of assessing airways function in the clinic cannot reliably evaluate its presence. However, most recently, promising methods of assessment are being utilised.

Methods: We conducted a systematic literature review, using PubMed, with the aim of determining the prevalence of small airways disease in adult patients with asthma. We ascertained how small airways disease prevalence compared between different studies when measured using distinct techniques of small airways assessment.

Results: Fifteen publications were identified determining the prevalence of small airways disease in asthma. Methods of assessments included impulse oscillometry, spirometry, body plethysmography, multiple-breath nitrogen washout, and high-resolution computed tomography. These studies used differing inclusion characteristics and recruited patients with a broad range of asthma severity, yet collectively they reported an overall prevalence of small airways disease of 50–60%. Small airways disease was present across all asthma severities, with evidence of distal airway disease even in the absence of proximal airway obstruction.

Conclusions: Small airways disease is highly prevalent in asthma, even in patients with milder disease. Given the clinical impact of small airways disease, its presence should not be underestimated or overlooked as part of the daily management of patients with asthma.

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1. Introduction

The small airways are usually defined as having an internal diameter smaller than 2 mm [1], and are generally understood to include the small airways conducting zone and the acinar zone (the terminal and respiratory bronchioles and alveolar ducts). Conventional methods of assessing airways function such as forced expiratory volume in 1 s (FEV₁) and peak expiratory flow (PEF), are influenced by the degree of airway resistance (which is largely due to the larger, proximal airways), and so cannot reliably and sensitively evaluate small airways obstruction. However, more recently, distinct physiological and imaging techniques are allowing an assessment of the ‘quiet zone’, and it is clear that small airways disease (SAD) contributes significantly to the clinical impact of asthma [2]. For example, small airways inflammation has been shown to correlate with symptoms in patients with nocturnal asthma [3], and with the Asthma Control Test (ACT) score even in patients with asthma of mild severity [4]. Furthermore, it has been observed that increased small airways resistance correlates with worsening health status [5], dyspnoea [5], and asthma exacerbations [6].

Moreover, pharmacological interventions have been developed that allow the delivered drug to reach the small airways, such as small particle (<2 micron) formulations [7]. These have been shown to improve SAD and improve outcomes in patients with asthma [8]. Vos et al. reported a statistically significant correlation ($p = 0.004$) between changes in small airways volume, determined from high-resolution computed tomography (HRCT), and patients’ asthma control following treatment with a small particle combination inhaled corticosteroid (ICS) and long-acting β_2 -agonist (LABA) [9]. Hoshino treated patients who had mild-persistent asthma with conventional-particle ICS monotherapy for 8 weeks, and then randomized them to either continue conventional-particle ICS or switch to a small-particle ICS [10]. The small-particle ICS led to a significant improvement in small airways resistance, determined by impulse oscillometry (IOS), and the patients’ ACT score, which was not observed with conventional-particle ICS treatment. Farah et al. found that baseline small airways ventilation, assessed using multiple-breath nitrogen washout, predicted patient’s symptomatic response to ICS titration [11]; and changes in the Asthma Control Questionnaire (ACQ)-5 score correlated with changes in small airways ventilation [12]. Recently, ‘real-life’ studies have also demonstrated better asthma control with small particle ICS monotherapy or ICS/LABA combination formulations compared with conventional-particle aerosols [8,13,14].

1.1. Search methodology

Given the increasing awareness of the importance of SAD in asthma management, we conducted a systematic literature review to determine the prevalence of SAD in adult patients with asthma, and to ascertain how SAD prevalence compared between different studies when measured using different methods of assessment. A number of other reviews have considered the practical application of these techniques in determining SAD [2,7,8], and so this was not an aim of this current work. The literature search, using PubMed, was conducted by one of the researchers on 21 December 2015 (for manuscripts published up to that date) with the phrase “small

airways” OR “distal lung” OR “peripheral airways” AND asthma (with the only limit applied being for English language). Abstracts were scanned for potential relevance (i.e., potentially containing data from a clinical trial on the prevalence of SAD in adults with asthma), with shortlisted manuscripts reviewed in detail for data on the percentage of the population with SAD (as defined by the authors of each source manuscript), either using the percentages quoted in the manuscripts, or calculating a percentage using quoted patient numbers. A second researcher then performed a quality check on the shortlisted manuscripts, and discussed any discrepancies with the first researcher. The data are reported for individual studies with no data synthesis, and the Cochrane Collaboration’s tool was used to assess the risk of bias. The search protocol is registered on the PROSPERO register of systematic reviews, registration number CRD42015026971. Only data reporting on the prevalence of small airways disease were assessed.

2. Overview of reported techniques

2.1. Spirometry, plethysmography and volume assessment

Premature airways closure is a feature of SAD, resulting in air-trapping and hyperinflation. Forced vital capacity (FVC) is an indirect marker, with reduced values indicating the presence of SAD [15]. The difference between slow vital capacity (SVC) and FVC has also been utilised as an indirect marker of air-trapping [16]. In addition, lower values of forced expiratory flow (FEF) from 25 to 75%, or at 50% or 75% (FEF_{25–75%}, FEF_{50%}, FEF_{75%}) have been reported to suggest the presence of small airways obstruction [16]. However, these parameters may simply reflect airflow heterogeneity, and should ideally be supported by other physiological or imaging investigations to confirm the presence of SAD [16].

Body plethysmography is more sensitive for detecting small airways obstruction than the forced expiratory flow measures [17]. Higher values of functional residual capacity (FRC), residual volume (RV), or the ratio of RV to total lung capacity (TLC) indicate lung hyperinflation, which is suggestive of the presence of SAD.

Finally, some researchers have used either closing capacity (CC) or closing volume (CV) to determine the presence of small airways disease, indicated by an increase in either CV/VC or CC/TLC.

2.2. Impulse oscillometry

IOS utilises pressure applied to the airways at a range of frequencies, and components of respiratory impedance are measured, including resistance and reactance [18]. Resistance at 5 Hz (R5) and 20 Hz (R20), respectively, represent total airway resistance and proximal airway resistance. The difference between these two values can be calculated (R5–R20), with higher values suggesting the presence of SAD.

2.3. Multiple-breath nitrogen washout

Gas is transported in the lung by either convection in the larger airways, or diffusion in the smaller acinar airways, with the border between these two mechanisms of gas transport corresponding to the end of the terminal respiratory bronchioles. Multiple-breath nitrogen washout utilises this to assess ventilation heterogeneity, with S_{cond} associated with the conductive airways, and S_{acin} with

acinar structures [19]. Higher S_{acin} values indicate ventilation heterogeneity, suggestive of distal acinar SAD; SAD can also contribute to elevated S_{cond} values.

2.4. High-resolution computed tomography

Individual acini are not generally visible using HRCT. However, air-trapping can be detected using HRCT conducted at end-expiration, seen as parenchymal areas with a less than normal increase in attenuation [20]. Diffuse or subtle air-trapping may require the operator to compare inspiratory and expiratory scans.

3. Results

Of 837 articles identified, fifteen had relevant content (Fig. 1 and Table 1) [21–35]. Eleven of these were identified from the PubMed search; one was quoted in the discussion section of an identified article; and the authors of the current manuscript suggested three additional publications that were not identified in this search. The prevalence of SAD in the individual studies is summarized in Fig. 2. Interestingly, although 24 studies were identified that used exhaled nitric oxide to assess airways function, all presented data only as mean values, rather than the percentage above (or below) a specified cut-point, and so SAD prevalence could not be calculated.

Using the Cochrane Collaboration's tool for assessing the risk of

bias, in terms of the data reported here, we consider the risk of bias to be low in nine of the studies, and low-to-medium in the remainder (due to possible selection bias). It should be noted that the majority of the studies did not report blinding of participants, personnel or outcome assessments, but given the outputs of interest are physiological, this is not considered to be a source of bias.

3.1. Prevalence using spirometry, plethysmography or volume assessments

Manoharan et al. used data from 442 patients undergoing screening for clinical trials. A cut-point of 60% of predicted for $FEF_{25-75\%}$ was used to define the presence of SAD – which the authors described as arbitrary [24]. A total of 238 patients (54%) had values <60%; these patients were significantly older and with a worse FEV_1 than those without SAD.

Jain et al. reviewed lung function data from 321 patients with predominantly mild airflow obstruction (only 25% having FEV_1 <80% of predicted) [23]. There was a high prevalence of air trapping, with 52% of the patients having abnormal RV (defined as >100% predicted), and 57% having abnormal RV/TLC ratios (defined as >35%). Furthermore, in the patients with FEV_1 <90% predicted, there was a trend to increasing RV and RV/TLC with decreasing FEV_1 .

Perez and colleagues analysed lung function data from 222

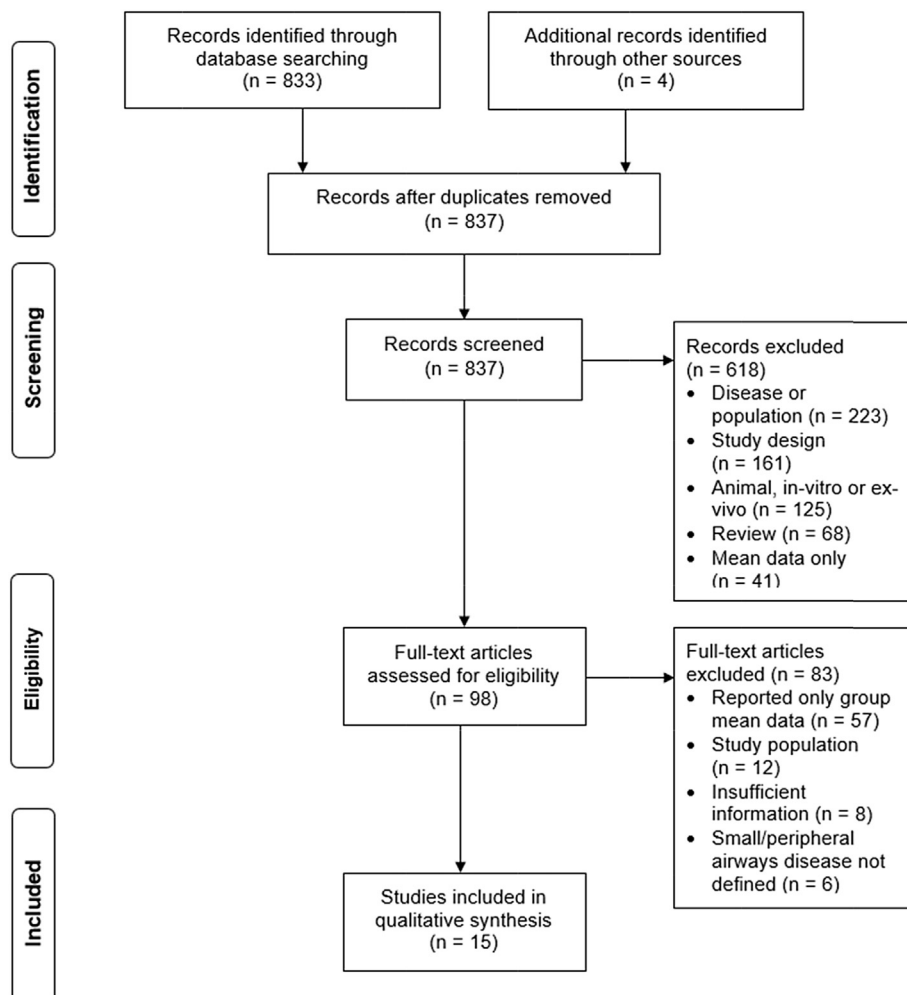


Fig. 1. PRISMA 2009 flow diagram.

Table 1
Summary of studies assessing prevalence of small airways disease.

Method	Study	Population				Endpoint
		Asthma severity	Sample size	Age (years) ^a	FEV ₁ (percent predicted) ^a	
Spirometry, plethysmography and volume assessment	Manoharan et al. [24]	All severities	n = 442	42 ± 15	86 ± 20	FEF _{25–75%} <60% predicted RV >100% predicted RV/TLC >35 One or more of: • FRC >120% pred. • RV > pred. + 1.64 RSD • RV/TLC > pred. + 1.64 RSD • FEF _{25–75%} < pred. – 1.64 RSD • FEF _{50%} < pred. – 1.64 RSD • SVC–FVC >10% One or more of: • FRC >120% pred. • RV > pred. + 1.64 RSD • RV/TLC > pred. + 1.64 RSD SVC–FVC >10% RV > predicted + 1.64 RSD FRC >120% predicted FEF ≤LLN CC/TLC more than 2 SD of that of a group of normal healthy adults CV/VC above normal limits (defined as variation greater than 20% of predicted) R5–R20 > 0.030 kPa s L ^{−1} R5–R20 > 0.030 kPa s L ^{−1}
	Jain et al. [23]	No restriction	n = 321	47.9 ± 13.6	84.9 ± 20.1	
	Perez et al. (2013) [25]	Moderate to severe; <u>without</u> proximal airways obstruction	n = 222	43.7 ± 16.1	97.7 ± 24.8	
		Moderate to severe; <u>with</u> proximal airways obstruction	n = 219	Not stated	64.3 ± 38.1	
	Perez et al. (2012) [26]	Poorly controlled and/or significant dyspnoea	n = 324	49 ± 17	75 ± 18	
	Telenga et al. [28]	Mild to moderate, receiving ICS	n = 94	43 (33–53) ^c	83.4 (70.9–89.5) ^c	
	Kulpati et al. [35]	Asymptomatic (FEV ₁ /FVC>0.7)	n = 25	27.9 ± 7.4	Not reported (2.69 ± 0.37 L)	
	McCarthy et al. [34]	Stable	n = 19	Range 21–50 (mean not reported)	56–112 (mean not reported)	
Impulse oscillometry (IOS)	Alfieri et al. [21]	Mild to moderate	n = 63	42 ± 14	92 ± 14	R5–R20 > 0.10 kPa s L ^{−1} R5–R20 ≥ 0.075 kPa s L ^{−1} S _{acin} > ULN, defined as mean + 1.64 SDs in age-matched control (0.204 L ^{−1}) S _{acin} >0.12 L ^{−1}
	Anderson et al. [22]	British Thoracic Society (BTS) Steps 2 to 4	n = 378	BTS Step 2: 39 (37, 41) ^b BTS Step 3: 41 (38, 45) ^b BTS Step 4: 44 (42, 47) ^b	BTS Step 2: 89.8 (87.5, 92.2) ^b BTS Step 3: 86.3 (81.7, 90.8) ^b BTS Step 4: 83.7 (79.6, 87.8) ^b	
Multiple or single-breath nitrogen washout [36]	Manoharan et al. [24]	All severities	n = 442	42 ± 15	86 ± 20	S _{acin} >0.12 L ^{−1} S _{acin} percent predicted >ULN
	Pisi et al. [27]	All severities	n = 33	45 ± 15	100 ± 11	
	Gonem et al. [31]	GINA Steps 3 to 5	n = 37	S _{acin} normal 54.2 ± 3.1 S _{acin} high 61.2 ± 1.9	S _{acin} normal 83.9 ± 3.8 S _{acin} high 65.4 ± 4.8	
	Hanon et al. [32]	Receiving ≤800 µg/day of budesonide or equivalent	n = 66	52 ± 17	76 ± 19	
	Verbanck et al. [33]	Receiving budesonide	n = 30	43±3 ^d	75±4 ^d	
	Thompson et al. [29]	During asthma exacerbation, compared with stable asthma	Exacerbation n = 18 Stable n = 19	Exacerbation: 33 (25–55) ^e Stable: 56 (48–61) ^e	Exacerbation: 59 (45–75) ^e Stable: 78 (70–85) ^e	
HRCT	Tunon-de-Lara et al. [30]	Uncontrolled mild or moderate	n = 45	35.3 ± 10.7	89.2 ± 15.9	Air-trapping according to the definition of the Fleischner Society [37]

FEV₁ = forced expiratory volume in 1 s; FEF = forced expiratory flow; RV = residual volume; TLC = total lung capacity; FRC = functional residual capacity; RSD = residual standard deviation; SVC = slow vital capacity; FVC = forced vital capacity; ICS = inhaled corticosteroid; LLN = lower limit of normal; CC = closing capacity; CV = closing volume; IOS = impulse oscillometry; R5 = total airway resistance; R20 = proximal airway resistance; S_{acin} = acinar ventilation heterogeneity; SD = standard deviation; ULN = upper limit of normal; HRCT = high-resolution computed tomography.

^a Mean ± standard deviation, unless stated otherwise.

^b Mean and 95% confidence interval (CI).

^c Median and interquartile range.

^d Mean ± standard error of the mean.

^e Median and 95% CI.

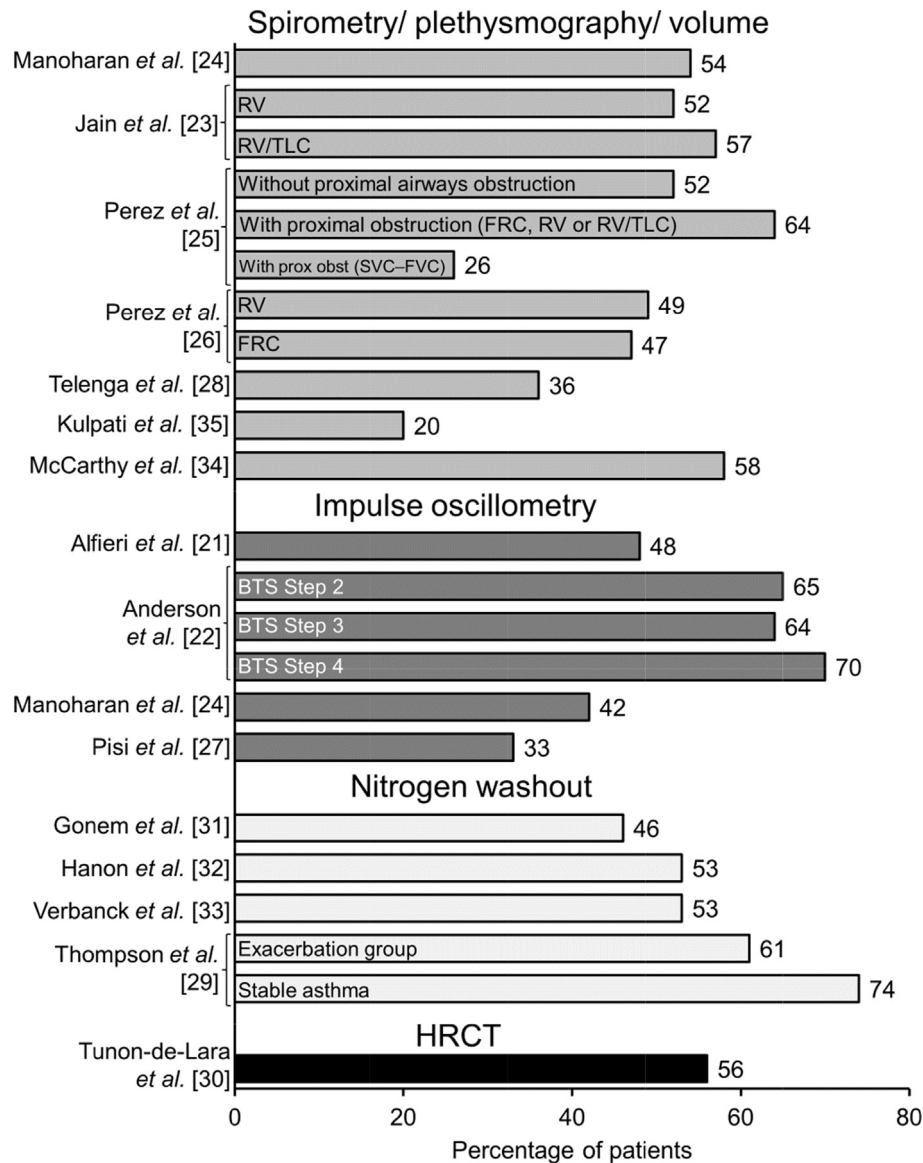


Fig. 2. Prevalence of small airways disease in reviewed studies.

patients without large airways obstruction (defined as $FEV_1 \geq 80\%$ of predicted and $FEV_1/FVC \geq 0.7$) [25]. SAD was defined as the presence of one or more of the parameters listed in Table 1, and was observed in 115 (52%) of these patients. The incidence of individual SAD criteria is shown in Fig. 3; the three hyperinflation criteria were more common than airflow limitation (using $FEF_{25-75\%}$) or expiratory trapping.

A separate study by Perez et al. assessed the presence of hyperinflation (based on RV or FRC criteria) in 324 patients with either poorly controlled asthma (defined by the authors as ACT <20) or significant dyspnoea (Medical Research Council dyspnoea score ≥ 1) [26]. Of the 324 patients, 49% had evidence of hyperinflation according to RV, with 47% meeting the FRC criterion. Although the prevalence was higher in patients with a lower FEV_1 percent predicted (78 and 70% for RV and FRC, respectively, in patients with $FEV_1 < 60\%$ predicted), hyperinflation was observed in more than a third of patients with normal airflow (34 and 40%, respectively, in patients with $FEV_1 > 80\%$ predicted), which the authors suggest indicates the involvement of small airways.

Telenga et al. assessed the prevalence of small airways obstruction in 94 patients with mild to moderate asthma receiving ICS therapy [28]. The parameter used was FEF below the lower limit of normal; 34 of the patients (36%) met this criterion. This subset of patients required a significantly higher dose of ICS than the group with normal FEF values, and had more severe bronchial hyper-responsiveness (assessed using a histamine challenge).

Two slightly older studies used either CC or CV to indicate the presence of SAD. In the first study, McCarthy et al. recruited 19 patients with asthma during a symptom-free period [34]. Of these, eleven (57.9%) had an increased CV/VC ratio (defined as variation greater than 20% of predicted). The investigators were unable to determine the CV in a further five patients – including these in the definition of SAD increased the prevalence to 84%. In the second study, Kulpati et al. recruited 100 subjects into four groups – 25 normal, healthy adults, 25 asymptomatic smokers, 25 patients with asymptomatic asthma, and 25 symptomatic smokers [35]. All participants had to have $FEV_1/FVC > 70\%$. Within the asthma group, 5/25 (20%) had CC/TLC% more than 2 SD of that of the healthy

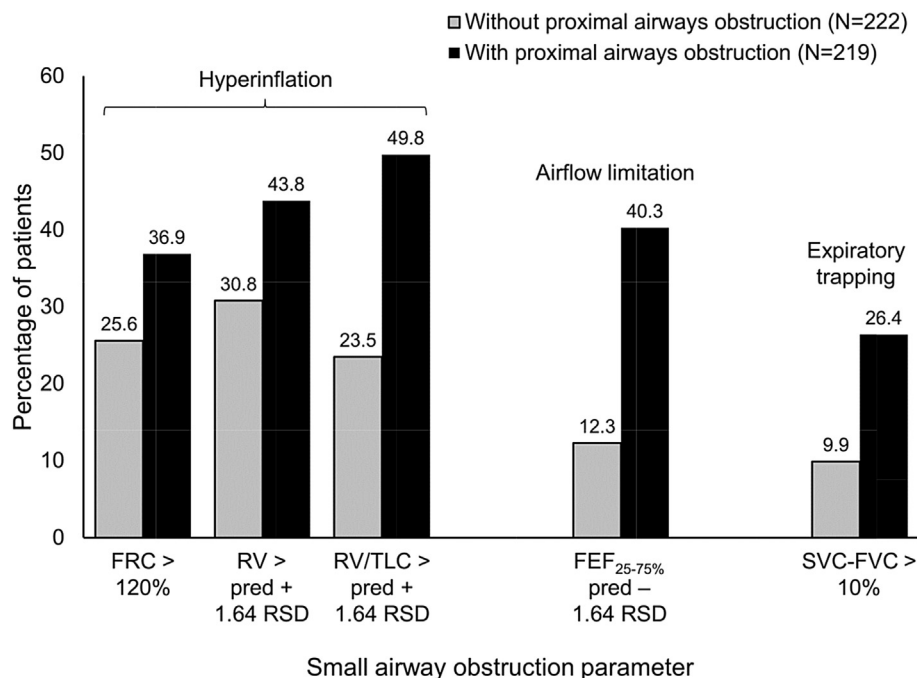


Fig. 3. Incidence of small airways obstruction by individual parameters in a population without (grey bars) or with (black bars) proximal airways impairment (adapted from Perez et al. [25]).

participants. The authors suggest that CC/TLC is more sensitive than CV/VC for detecting small airways dysfunction.

3.2. Prevalence using impulse oscillometry

Alfieri et al. recruited 63 patients with mild-to-moderate asthma, defining SAD as R5–R20 above the upper limit of normal (ULN) of 0.030 kPa s L⁻¹ [21]. Thirty patients (47.6%) met this definition; these patients were older, more likely to be female, non-atopic and to have uncontrolled asthma (ACT score ≤19). Anderson et al. also used R5–R20 > 0.030 kPa s L⁻¹ in their retrospective analysis, describing this threshold as ‘the upper bound of the 95% CI in a previously reported group of healthy subjects’ [22]. Patients were stratified by British Thoracic Society (BTS) management stage: Step 2 (low-to-moderate ICS dose); Step 3 (low-to-moderate ICS dose plus a second controller); Step 4 (high dose ICS), with the prevalence of abnormal R5–R20 values being 64.6%, 63.5% and 69.9%, respectively.

In contrast, Pisi et al. used a value of 0.075 kPa s L⁻¹ as the threshold for SAD, describing this as ‘a conservative upper limit of normal’ [27]. They recruited 33 patients with normal FEV₁, 11 of whom (33%) met the criterion for SAD. In all patients, R5–R20 was significantly ($p < 0.05$) related to the ratio of FVC/SVC, FEF_{25–75%} and ACT. Fourteen of the 33 patients had at least one mild to moderate exacerbation in the prior year; SAD prevalence was significantly higher ($p = 0.013$) in the exacerbators (57%), compared to the non-exacerbators (19%).

In the analysis of data from patients undergoing screening for clinical trials mentioned in the previous section, Manoharan et al. also used an arbitrary R5–R20 cut-point of 0.1 kPa s L⁻¹ to define the presence of SAD [24]. Of the 442 patients analysed, 185 (42%) had evidence of SAD. These patients were significantly older, with worse lung function (FEV₁ and FEF_{25–75%}) than those without SAD.

3.3. Prevalence using nitrogen washout

Gonem et al. recruited 37 patients with asthma and 17 age-matched healthy controls, defining the ULN for S_{acin} as the mean + 1.64 SDs in the control group – a value of 0.204 L⁻¹ [31]. Using this value, 17 of the patients with asthma (46%) had high S_{acin}. Compared with the patients with asthma and no SAD, these patients were significantly more likely to have lower FEV₁% predicted and FEV₁/FVC, and higher FRC, RV/TLC and lung clearance index.

Hanon et al. investigated switching patients with stable asthma from a conventional-particle ICS formulation to a small particle ICS formulation [32]. Eligible patients had abnormal S_{acin}, defined as >0.12 L⁻¹ at the study screening visit. The researchers screened 66 patients to recruit 35 eligible patients – suggesting a prevalence of abnormal values of 53%.

A S_{acin} cut-off of 0.12 L⁻¹ was also used by Verbanck et al. in a study of 30 patients with a wide range of asthma severities, all receiving a dry powder formulation of budesonide for at least 6 weeks prior to entry [33]. Sixteen patients (53%) had abnormal baseline S_{acin} values. On being switched from the dry powder to an aerosol formulation preferentially distributed to the peripheral airways [38], there was a significant improvement ($p < 0.05$) in mean S_{acin} in the group with abnormal baseline S_{acin} values, but no change in the group with normal values.

Thompson et al. recruited 18 consecutive patients admitted to a hospital with severe asthma exacerbations, conducting spirometry and multiple-breath nitrogen washout tests within 48 h of admission [29], and defined SAD as S_{acin} above the ULN from an earlier study [39]. Nineteen patients with stable asthma (ACQ<0.75) were recruited for comparison. Of the patients admitted for an exacerbation, 11 (61%) had S_{acin} >ULN; this was not significantly different to the stable asthma controls, in whom 14 (74%) had values >ULN. When the two groups of patients were combined, there was a significant relationship between S_{acin} and FEV₁ percent predicted (Spearman rank order correlation coefficient, $r_s = -0.57$, $p < 0.001$), although even some patients with normal FEV₁ values had

evidence of SAD. There was also a significant relationship between Global Initiative for Asthma (GINA) 2011 Step and S_{acin} in the exacerbation group ($r_s = 0.59$, $p = 0.016$); a regression analysis was not performed in the stable asthma group as most of the patients were in GINA Steps 3 or 4.

3.4. Prevalence using HRCT

In the only study identified that reported prevalence using HRCT, 58 patients with uncontrolled mild or moderate asthma were recruited [30]. HRCT evaluations were conducted, and patients with air-trapping were randomized to different ICS treatments. The authors report demographic data for 20 patients without air-trapping and 25 patients with air trapping, suggesting a SAD prevalence of 56%. There were no significant differences between these groups for any demographic characteristics.

4. Discussion

The small airways are currently highly topical, with the resurgence of interest in assessing the 'silent zone' driven by enhanced physiological and imaging detection systems, coupled with innovation in pharmaceuticals to target inhaled drugs to this region, in order to evaluate the relevance of this area in day-to-day clinical practice [2,8]. Although evidence from clinical trials on treatment targeted to the small airways is mixed, 'real life' research has shown potential benefit on asthma control and quality of life [13,14], where the corticosteroid dose can be significantly reduced with small particles and achieve as good an effect as large particles. However, there are limited data available on the prevalence of small airways disease in patients with asthma.

To our knowledge this is the first systematic literature review to assess the prevalence of SAD in patients with asthma. We ascertained that most studies consistently observed between 50 and 60% of patients with asthma displaying evidence of SAD, with SAD existing across the entire spectrum of asthma severity, including patients with normal FEV_1 [29], and patients with little or no proximal airflow obstruction [25]. This supports the notion that conventional spirometric methods of assessing airways function in the clinic cannot reliably and sensitively evaluate small airways dysfunction.

It is apparent in our review that there is variation in the selection of endpoints used to define the presence of SAD. Different researchers use different threshold criteria for the same endpoints, including population values, disease-specific or study-specific, and (arbitrary) fixed values. Further, the studies that used more sensitive measures of airway function (such as IOS, nitrogen washout and HRCT) tended to recruit smaller numbers of patients. To add to this complexity, the reported studies recruited populations with very different patient characteristics. Indeed, Anderson et al. found the prevalence of SAD in patients with populations of differing asthma severity, as defined by their need for asthma treatment, was approximately two-thirds across all BTS treatment steps 2–4, despite all patients in these steps having a normal FEV_1 , suggesting that conventional inhaled therapy was unable to attenuate SAD [22]. Unfortunately the study by Anderson et al. was the only one to report prevalence data for different disease severities, and this study did not recruit patients with mild, intermittent (i.e., BTS treatment step 1) asthma. We are therefore unable to estimate whether prevalence could be higher in very mild or very severe disease – and are also unable to conclude on the relative prevalence of SAD in different levels of asthma severity using other methods.

Another question that has been raised is whether SAD occurs when inflammation is present, or when there is functional

impairment. A number of studies have shown that tissue inflammation in the small airways correlates with symptoms. For example, Kraft et al. evaluated the level of inflammatory cells taken from bronchial biopsies, showing that the levels in the alveolar tissues (and not proximal tissues) correlated with nocturnal symptoms [3]. This is supported by data showing that small particle ICS improve symptoms compared with standard particle ICS (suggesting that the effect is at least partly due to reduced inflammation in the small airways) [10]. Other studies, including Manoharan et al., have shown that functional measures of SAD correlate with the extent of symptoms and asthma control [40]. It is likely, therefore, that the clinical impact of SAD is due to a mixture of inflammation and functional changes within the small airways.

Our systematic literature review has highlighted the need for a 'gold standard' definition for SAD. The methodological techniques used in these studies to identify SAD are indirect assessments, with few evaluations able to directly measure disease in the small airways. Unlike spirometry, which over many decades has led to the development of population data on measures such as FEV_1 that are utilised as endpoints in clinical trials and in respiratory diagnosis, many of the SAD assessments are in their relative infancy, although population data is being generated [41–43].

Although none of the identified studies used FVC alone to evaluate the prevalence of SAD, in a study of patients enrolled into the National Heart, Lung, and Blood Institute's Severe Asthma Research Program, there was a statistically significant correlation between FVC and RV/TLC (Pearson correlation coefficient, $r = -0.64$; $p < 0.0001$) [44]. This suggests (at least at a group level) that FVC might have some utility in assessing SAD, especially since FVC can be easily assessed by primary care physicians, so could be undertaken as a serial assessment to monitor SAD. Indeed, FVC is considered to have high reproducibility and low variability, correlating well with small airways obstruction, in contrast to $FEF_{25-75\%}$, which has low reproducibility and is influenced by large airway obstruction. In the only study to determine the prevalence of SAD by both IOS and spirometry, Manoharan et al. reported values of 42% using IOS and 54% using $FEF_{25-75\%}$, suggesting that the two methods are not comparable – although admittedly this analysis used arbitrary values to define the presence of SAD [24]. In contrast, Pisi et al. [27] showed that R5–R20 was significantly ($p < 0.05$) related to FVC/SVC and $FEF_{25-75\%}$, suggesting that these spirometric parameters can at least give an indication of the presence of SAD. However, in the study by Perez et al., in patients without proximal airways impairment SAD prevalence according to airflow limitation (i.e., $FEF_{25-75\%}$) was under-reported in comparison to hyperinflation criteria, suggesting that spirometry (specifically FEF) is a relatively inaccurate method of determining the presence of SAD [25]. Indeed, the American Thoracic Society has advised that $FEF_{25-75\%}$ should not be used to diagnose SAD [45], and the FEF-based prevalence data that we present here therefore need to be interpreted with caution. In contrast, closing volume (from single nitrogen washout) has been shown to have good sensitivity to detect small airways inflammation, even relatively early in the pathologic process [46]. However, such measurements are not commonly used in everyday clinical practice as they are complex to administer and interpret, and have a high degree of variability compared to FEV_1 .

Indeed, in a similar manner to composite scoring systems such as the BODE index in COPD [47] to identify particular patient characteristics, work is currently underway to determine whether composite indices of SAD may identify a small airways phenotype. Indeed, one study has suggested that IOS (described as effort-independent) and spirometry (effort-dependent) may provide 'distinct yet complimentary' data on the presence and impact of SAD, which suggests that combining these types of measures into a

composite index might have utility [40]. A small airways 'phenotype' has previously been described as being individuals with not optimally controlled asthma (ACQ >1.5, symptoms, regular use of reliever medication, or failure to respond to ICSs and LABAs), but with relatively normal spirometry values [16]. Although in the HRCT study there were no differences in demographic characteristics between the groups with or without air trapping [30], other studies have described correlations between SAD and asthma control (ACT score) [21], exacerbations [27], or bronchial hyper-responsiveness [28]. Despite the challenges in its measurement, these findings highlight the potential benefits of determining the presence of SAD, and could enable appropriate targeting of pharmacotherapy. The ongoing longitudinal Assessment of small Airways involvement In asthma (ATLANTIS) study will further enhance our knowledge of the prevalence of small airway disease in asthma [48].

In conclusion, studies conducted using different techniques to assess SAD collectively indicate that SAD is prevalent across the range of asthma disease severity, even in patients with milder disease. Given its clinical impact, the presence of SAD should not be underestimated or overlooked as part of the management of patients with asthma.

Conflict of interest

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MS and AB are full-time employees of Chiesi Farmaceutici SpA.

PB has served on Scientific Advisory Boards of AstraZeneca, Boehringer-Ingelheim, Bepak, Chiesi, Daiichi-Sankyo, GlaxoSmithKline, Glenmark, Johnson & Johnson, Merck, Novartis, Nycomed/Takeda, Pfizer, Prosonix, RespiVert, Sun Pharmaceuticals, Teva and UCB and has received research funding from Aquinox Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Chiesi, Daiichi-Sankyo, GSK, Novartis, Nycomed/Takeda, Pfizer, Prosonix, and Sun Pharmaceuticals. He is also a cofounder of RespiVert (now part of Johnson & Johnson), which has discovered novel inhaled anti-inflammatory treatments for asthma and COPD.

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