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Original Research

Small airway dysfunction in asthmatic patients treated with as-needed SABA monotherapy: A perfect storm

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ABSTRACT

Background: Short-acting beta agonist (SABA)-only treatment is associated with poor asthma control and adverse clinical outcomes. The importance of small airway dysfunction (SAD) is increasingly recognized in asthma, but less is known in patients using SABA-only therapy. We aimed to investigate the impact of SAD on asthma control in an unselected cohort of 60 adults with physician-diagnosed intermittent asthma treated with as-needed SABA monotherapy.

Methods: All patients underwent standard spirometry and impulse oscillometry (IOS) at the first visit and were stratified by the presence of SAD defined by IOS (fall in resistance 5–20 Hz [R5-R20]>0.07 kPa × s*L^{-1}). Univariable and multivariable analyses were used to analyze cross-sectional relationships between clinical variables and SAD.

Results: SAD was present in 73% of the cohort. Compared with patients without SAD, adults with SAD had a higher number of severe exacerbations (65.9% versus 25.0%, $p < 0.05$), higher use of annual SABA canisters (median (IQR), 3 (1.75–3) versus 1 (1–2), $p < 0.001$), and significantly less well-controlled asthma (11.7% versus 75.0%, $p < 0.001$). Spirometry parameters were similar between patients with IOS-defined SAD and those without SAD. The multivariable logistic regression analysis showed that exercise-induced bronchoconstriction symptoms (EIB, odds ratio [OR] 31.18; 95%CI:4.85–365.00) and night awakenings due to asthma (OR 30.30; 95%CI:2.61–1141.00) were independent predictors of SAD, with a high predictive power of the model incorporating these baseline predictors (AUC 0.92).

Conclusions: EIB and nocturnal symptoms are strong predictors of SAD in asthmatic patients using as-needed SABA-monotherapy, helping to distinguish subjects with SAD among patients with asthma when IOS cannot be performed.

1. Introduction

Asthma affects approximately 339,000,000 people worldwide [1]. As-needed treatment with short-acting β2-agonists (SABA) has traditionally been used for symptom relief across all severities of asthma, and as monotherapy in patients with mild asthma [2].

Abbreviations: SAD, Small airway dysfunction; FeNO, Fractional exhaled nitric oxide; BMI, Body Mass Index; FEV1, Forced expiratory volume in the first second; FVC, forced vital capacity; FEF25-75, Forced Expiratory Flow Between 25% and 75%; R5-R20, Resistances at 5 and 20 Hz; X5, Reactance at 5 Hz; Ax, Reactance area; FRes, Resonant frequency in Hz; ΔX5, difference between inspiratory and expiratory X5.

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A recent study indicates an association between high SABA prescriptions and poor clinical outcomes across a broad range of countries, healthcare settings, and asthma severities [3]. Regular use of SABA, even for 1–2 weeks, is associated with multiple adverse effects, including β-receptor down-regulation, decreased broncho-protection, rebound hyperresponsiveness [4], decreased bronchodilator response [5], increased allergic response [6], and increased eosinophilic airway inflammation [7]. Independent of maintenance therapy, increasing SABA exposure leaves patients at risk of severe exacerbations. In the United States, SABA monotherapy is the most frequently used by asthmatics, with over half experiencing one or more annual severe exacerbations [8]. Indeed, the Global Initiative for Asthma (GINA) guidelines do not recommend the use of SABA monotherapy for Step 1 in adults and adolescents with asthma anymore, because of the risks associated with SABA-only treatment and overuse, and evidence for benefit of inhaled corticosteroids (ICS) [9].

In asthma, small airway dysfunction (SAD) is associated with more severe airway hyperresponsiveness, worse disease control, and a higher number of exacerbations [10–18]. Overall, the prevalence of SAD in asthmatics is around 50–60% across all GINA severity stages [15–18], but consistently higher in more severe asthma (GINA step 4–5) [10,19,20]. These frequencies also vary based on the measuring method, with spirometry being less sensitive in detecting SAD [21,22]. In recent years more specialized tests have been developed, which may better assess SAD [18]. Impulse oscillometry (IOS) is an effort-independent test, based on the well-described forced oscillation technique (FOT) [23,24], which has emerged as a sensitive method to measure pulmonary function and evaluate small airways [18,25,26].

Despite being associated with worse asthma control and risk of exacerbations, the impact of SAD on asthma patients using SABA monotherapy has never been addressed. In this study, we aimed to investigate, the prevalence, impact on asthma control, and clinical characterization of IOS-defined SAD in an unselected sample of adults with intermittent asthma treated with as-needed SABA only.

2. METHODS

2.1. Patients and study design

This is a cross-sectional analysis of a single-centered, observational study on 60 adults (≥18 years old) with physician-diagnosed asthma, consecutively recruited between September 1st, 2019 and May 1st, 2022. All patients were in GINA Step 1 with SABA-monotherapy and had stable asthma (i.e., without worsening symptoms of wheezing, breathlessness, chest tightness, and coughing) at the time of the visit and during the 4 weeks before recruitment. Patients fulfilling the criteria for asthma/chronic obstructive pulmonary disease overlap syndrome were excluded [9].

Those who were unable to perform either acceptable spirometry (according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 guidelines) [27] or IOS (according to the standard recommended by ERS) [28] were also excluded. All patients underwent fractional exhaled nitric oxide (FeNO), IOS, and standard spirometry measurements at the same initial screening visit in the asthma clinic. Demographic parameters, clinical features (i.e., concomitant atopy, asthma duration, and eosinophil count), use of SABA (number of dispensing canisters in the previous year; 200 puffs per canister), and control as defined by GINA guidelines [9] were also recorded at the first visit. GINA assessment of asthma control includes the following symptoms in the 4 preceding weeks: daytime asthma symptoms more than twice a week, nighttime asthma symptoms, activity limitation, and use of short-acting b2-agonist more than twice a week. The resulting asthma control is classified as well-controlled (no symptoms), partially controlled (1–2 symptoms), and uncontrolled (≥3 symptoms) [9].

The most recent eosinophil count during the 2 years before the first assessment was also collected. Patients were defined as atopic if a positive skin prick test result to aeroallergens or specific IgE on peripheral blood and symptoms consistent with allergic asthma were present (i.e., asthma triggered by aeroallergens). If the atopic background was not known, patients underwent skin testing with a common standardized allergen panel of indoor and outdoor allergens, as recommended for clinical use and research in Europe [29].

This study was approved by the local institutional review board (institutional review board no. NP3364). All patients gave written informed consent for their data to be stored electronically. The study was conducted according to STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort, case-control, and cross-sectional studies.

2.2. FeNO

FeNO was performed in duplicate using HypAir FeNO (Medi-Soft, Sorinnes, Belgium), at a standard flow rate of 50 mL/s, according to the manufacturers and American Thoracic Society guidelines [30].

2.3. Lung function measurements

A Vyntus PNEUMO-PC Spirometer (VyAire Medical, Chicago, Ill) was used to perform spirometry in triplicate following the European Respiratory Society guidelines [27,31]. IOS (Masterscreen IOS/Sentry Suite, VyAire Medical) was performed in triplicate following the manufacturers and the European Respiratory Society guidelines [28,32,33]. The presence of SAD was defined by IOS as a fall in resistance from 5 to 20 Hz [R5–R20] >0.07 kPa × s*L^{-1}, as previously reported [17,34,35]. Moreover, data on the following variables were collected: resistance at 5 Hz (R5, in kPa × s*L^{-1}), which is an index of total airway resistance; reactance at 5 Hz (X5, in kPa × s*L^{-1}), which reflects elastic recoil of the peripheral airways; resonant frequency (Fres, in Hz), which is defined as the frequency at which the inertial properties of the airway and the capacitance of lung periphery are equal; reactance area (AX, the area under the reactance curve, in kPa/L), which reflects the elastic properties of the lung periphery and shown to be correlated with resistance at lower frequencies; the difference between inspiratory and expiratory X5 (Delta X5), which reflects expiratory flow limitation (EFL) [32,35–37].

The IOS system and spirometry are routinely calibrated, as suggested by the manufacturers [38].

3. Statistical analysis

Categorical data were summarized as percentages; significant differences or associations were analyzed using the chi-squared test, using the asymptotic or the simulated p-value. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), according to the result of the Shapiro-Wilk test for normality. With normality, comparisons between groups were performed with either Student's t-test for independent samples (2-tailed) or with ANOVA comparisons with Holm correction when more than two means were being compared. Without normality, comparisons were performed with the Mann-Whitney rank-sum test for independent samples (2-tailed) or with the Kruskal-Wallis test with Holm correction for more than two groups. The correlations between quantitative variables were assessed using Spearman correlation coefficients. A logistic regression model was fitted to study the effects of covariates on SAD, using a stepwise forward selection. Model performance was then assessed with the ROC curve and the corresponding AUC, and with the Hosmer–Lemeshow test for goodness of fit for logistic regression models. All the analyses were performed using the open-source software RStudio (www.rstudio.com), and a P value of less than 0.05 was considered statistically significant.

4. Results

4.1. Characteristics of the study population

We enrolled 61 patients, but we excluded one due to a recent pneumothorax, in which IOS and conventional PFT was not performed.

IOS-defined SAD was present in 73% of the cohort. Table 1 shows the demographic and clinical features of the study cohort, stratified by the presence of SAD. Subjects with SAD were more likely to be older and with higher BMI ($p < 0.05$). Only 11.5% of patients with SAD had well-controlled asthma, whereas most of the patients without SAD (75%) had well-controlled asthma. Furthermore, higher proportions of subjects with SAD had surrogates of a scarce asthma control compared with patients without SAD, namely exacerbation history, higher use of SABA (annual canisters), night awakenings due to asthma, and exercise-induced symptoms. By standard spirometry, only a minority (7%) of patients with SAD had larger airway involvement (as documented by FEV_1/FVC <70%), whereas values of FEF_{25-75} were not significantly different in patients with and without IOS-defined SAD.

4.2. Correlations between spirometry, IOS and asthma control

Spirometry parameters were similar between patients with IOS-defined SAD versus those without SAD ($p > 0.05$). Detailed standard spirometry and IOS measurements of subjects with and without SAD are summarized in Table 2. Focusing on the correlations between FEF_{25-75} and R5-R20, the standard spirometry and IOS indices conventionally used to assess peripheral airways resistance, a weak non-significant inverse correlation was observed (Table 3).

All asthma control categories had a different prevalence of SAD, with SAD being present in 100% of cases of uncontrolled (UC), 83% in partially controlled and 29% in well-controlled asthma (Table 4). Similarly, all IOS measurements, namely, resistance at 5 Hz, reactance at 5 Hz, R5-R20, reactance area, and resonant frequency, progressively worsened with the aggravation of asthma control categories (Table 4).

Table 1
Features of patients with asthma by the presence of SAD (defined as R5-R20 > 0.07).

Characteristics	SAD (n = 44, 73%)	NO SAD (n = 16, 27%)	*p-value*
Female sex, n (%)	29 (65.9%)	7 (43.7%)	0.2108
Age (y), median (IQR)	53 (39–63)	28.5 (24.5–46)	**0.0115**
BMI, (kg/m^2), median (IQR)	25 (22.75–29.25)	22.5 (21.75–29.25)	**0.0340**
Current or former smokers (>10 pack-years), n (%)	9 (20.5%)	6 (37.5%)	0.3333
Asma duration (y), median (IQR)	12 (5.75–17.0)	11 (3.75–16.5)	0.8536
Presence of atopy, n (%)	26 (59.1%)	14 (87.5%)	0.0793
Eosinophils (mm3), median (IQR)	347.5 (187.5–545.0)	210.0 (190.8–296.2)	0.3058
FeNO (ppb), median (IQR)	21.0 (16.5–40.8)	22.0 (14.5–36.8)	0.9867
Standard spirometry, n (%)			
FEV_1 < 80%	1 (2.3%)	1 (6.3%)	–
FEV_1/FVC <70%	3 (6.8%)	5 (31.3%)	**0.0244**
FEF_{25-75} <65%	5 (11.4%)	4 (25.0%)	0.2349
GINA asthma control, n (%)			**0.0005**
Well-controlled	5 (11.7%)	12 (75.0%)	
Partially controlled	20 (45.5%)	4 (25.0%)	
Uncontrolled	19 (43.2%)	0 (0%)	
Asthma exacerbations, n (%)	29 (65.9%)	4 (25.0%)	**0.0116**
Emergency room visit, n (%)	4 (9.0%)	0 (0%)	0.3288
Hospitalization, n (%)	2 (4.5%)	0 (0%)	0.6067
Night awakening due to asthma, n (%)	28 (63.6%)	1 (6.3%)	**0.0003**
EIB symptoms, n (%)	38 (86.4%)	3 (18.8%)	< **0.0001**
Annual SABA canisters, median (25–75%IQR) [range]	3 (1.75–3) [1–4]	1 (1–2) [1,2]	**0.0003**

IQR, interquartile range; FeNO: Fractional exhaled nitric oxide; BMI: Body Mass Index; FEV1: Forced expiratory volume in the first second; FVC: forced vital capacity; FEF25-75: Forced Expiratory Flow Between 25% and 75%. Comparisons were analyzed with chi-squared test (asymptotic or simulated p-value), and with Mann-Whitney test for independent samples (2-tailed). Significant *P*-values (<0.05) are represented in bold.

Table 2
Standard spirometry and IOS characteristics by the presence of SAD.

Patient features	SAD	NO SAD	*P*-value
Spirometry			
FEV_1% predicted	96.8 ± 12.7	97.8 ± 13.3	0.7908
FEV_1/FVC ratio (x 100)	79.2 ± 6.5	77.2 ± 9.2	0.3486
FEF_{25-75}% predicted	84.9 ± 26.8	79.9 ± 27.4	0.5315
IOS			
R5-R20 median (IQR)	0.17 (0.12–0.21)	0.03 (0.02–0.05)	< **.0001**
R5 mean ± SD	0.52 ± 0.15	0.33 ± 0.07	< **.0001**
X5 median (IQR)	−0.17 (−0.23–−0.15)	−0.10 (−0.12–−0.06)	< **.0001**
AX median (IQR)	1.58 (1.05–2.16)	0.27 (0.16–0.48)	< **.0001**
Fres median (IQR)	22.3 (18.5–24.9)	12.3 (9.6–14.9)	< **.0001**
Delta X5 median (IQR)	0.04 (0.02–0.12)	0 (−0.01–0.002)	**0.0001**

IQR: interquartile range; SD: standard deviation; FEV1: Forced expiratory volume in the first second; FVC: forced vital capacity; FEF25-75: Forced Expiratory Flow Between 25% and 75%; R5-R20: Resistances at 5 and 20 Hz; X5: Reactance at 5 Hz; Ax: Reactance area; Fres: Resonant frequency in Hz. ΔX5: difference between inspiratory and expiratory X5. Comparisons were analyzed with Student's t-test or with Mann-Whitney test for independent samples (2-tailed), according to the results of the Shapiro-Wilk test for normality. Significant P-values (<0.05) are represented in bold.

4.3. Baseline predictors of SAD

In the univariate analysis, the strongest predictors of SAD were EIB symptoms (odds ratio [OR], 25.12), night awakenings due to asthma (OR, 24.9), asthma control (OR, 20), age (OR, 6.6), FEV_1/FVC <0.7 (OR, 6.0), and asthma exacerbations (OR, 5.6) (Table 5). These variables were included in a multivariate logistic regression model using a backward stepwise method for model selection (Table 5). In the final fitted model, only EIB symptoms (OR 31.2; 95%CI:4.85–365; $p = 0.0013$) and night awakenings due to asthma (OR 30.3; 95%CI:2.61–1141; $p = 0.0205$) resulted being predictors of SAD. The fitted model was validated with the area under the curve (AUC = 0.92), indicating an excellent classification of the model and with the Hosmer and Lemeshow goodness of fit test (X-squared = 5.764, $p = 0.6737$) (Figure 1).

5. Discussion

In this study, we observed a high overall prevalence of IOS-defined SAD (73%) in adults with intermittent asthma treated with as-needed SABA monotherapy. Patients with SAD had a higher frequency of poor asthma control indicators (i.e. exacerbation history and use of SABA) than patients without SAD. R5-R20 and FEF25-75, which are, respectively, the IOS and spirometry parameters used to measure peripheral airway resistance, did not correlate, suggesting that SAD can be overlooked in asthmatic patients treated with as-needed SABA monotherapy when assessed only with conventional spirometry. SAD was present in 100% of the patients with uncontrolled asthma, whereas most of the patients without SAD had well-controlled asthma. Notably, we showed that EIB symptoms and nocturnal symptoms were independent predictors of SAD in GINA Step 1 patients, confirming previous studies focusing on more severe asthma patients [17,19,39].

Intermittent (GINA Step 1) asthma, i. e. asthma whose symptoms occur fewer than 2 days a week, is often treated with SABA monotherapy

Table 3
Correlations between functional parameters in patients with GINA Step 1 asthma.

	FEV1	FEV1/FVC	FEF25-75	R5	X5	R5-R20	AX	Delta X5
FEV1	1.0 (p < 0.001)	0.4 (p < 0.001)	0.6 (p < 0.001)	−0.4 (p = 0.002)	0.3 (p = 0.024)	−0.3 (p = 0.030)	−0.3 (p = 0.004)	−0.2 (p = 0.011)
FEV1/FVC	0.4 (p < 0.001)	1.0 (p < 0.001)	0.7 (p < 0.001)	−0.1 (p = 0.244)	0.0 (p = 0.897)	0.0 (p = 731)	−0.1 (p = 0.214)	0.0 (p = 0.503)
FEF25–75%	0.6 (p < 0.001)	0.7 (p < 0.001)	1.0 (p < 0.001)	−0.2 (p = 0.081)	0.2 (0.034)	−0.1 (p = 0.183)	−0.2 (p = 0.052)	−0.1 (p = 0.605)
R5	−0.4 (p = 0.002)	−0.1 (p = 0.244)	−0.2 (p = 0.081)	1.0 (p < 0.001)	−0.7 (p < 0.001)	0.8 (p < 0.001)	0.8 (p < 0.001)	0.6 (p < 0.001)
X5	0.3 (p = 0.024)	0.0 (p = 0.897)	0.2 (p = 0.034)	−0.7 (p < 0.001)	1.0 (p < 0.001)	−0.9 (p < 0.001)	−0.9 (p < 0.001)	−0.7 (p < 0.001)
R5-R20	−0.3 (p = 0.030)	0.0 (p = 0.731)	−0.1 (p = 0.183)	0.8 (p < 0.001)	−0.9 (p < 0.001)	1.0 (p < 0.001)	1.0 (p < 0.001)	0.7 (p < 0.001)

FEV1: Forced expiratory volume in the first second; *FVC*: *forced vital capacity*; *FEF25-75*: *Forced Expiratory Flow Between 25% and 75%*; *R5-R20*: *Resistances at 5 and* 20 Hz; *X5*: *Reactance at* 5 Hz; *Ax*: *Reactance area*; *Fres*: *Resonant frequency in Hz. ΔX5*: *difference* between inspiratory and expiratory X5. Correlations were analyzed with Spearman's test, p values are reported in brackets.

Table 4
IOS measurements and SAD prevalence by GINA control categories.

Measurement	Uncontrolled (n = 19)	Partially controlled (n = 24)	Well-controlled (n = 17)	*P*-value
R5, mean ± SD	0.57 ± 0.13	0.46 ± 0.15	0.35 ± 0.09	< **.0001**
X5, median (IQR)	−0.18 (−0.25–−0.17)	−0.17 (−0.21–−0.13)	0.11 (−0.13–−0.08)	< **.0001**
R5-R20, median (IQR)	0.20 (0.15–0.23)	0.14 (0.11–0.18)	0.06 (0.03–0.08)	< **.0001**
AX, median (IQR)	1.89 (1.25–2.28)	1.50 (0.82–2.07)	0.48 (0.21–0.64)	< **.0001**
Fres, mean (SD)	23.7 ± 4.8	19.5 ± 7.3	14.1 ± 5.9	**0.0001**
DeltaX5, median (IQR)	0.06 (0.02–0.12)	0.02 (0–0.07)	0 (−0.01–0.01)	**0.0002**
SAD, n (%)	100%	83%	29%	< **.0001**

IQR: interquartile range; SD: standard deviation; R5: Resistance at 5 Hz; R5-R20: Resistances at 5 and 20 Hz; X5: Reactance at 5 Hz; Ax: Reactance area; FRes: Resonant frequency in Hz. ΔX5: difference between inspiratory and expiratory X5.

One-way parametric or non-parametric ANOVA. All the pairwise comparisons using Student's t-test or Mann-Whitney test with Holm correction presented significant *P*-values (<0.05).

and is rarely considered the first step of a potentially evolving disease [3,5,7]. Intriguingly, our findings showed that the percentage of IOS-defined SAD in intermittent asthma is substantially high when compared to previous articles on more severe asthma (slightly more than 50%) [10,17] and that peripheral airway resistance (R5-R20) is as high

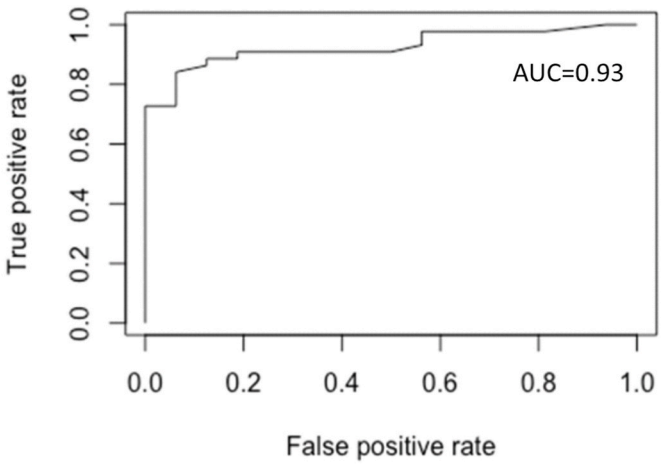

Fig. 1. Receiver operating characteristic (ROC) curve showing the ability of the model (two predictor-model: EIB and night awakenings due to asthma) to distinguish SAD from no SAD in patients with GINA Step 1 asthma. Features of patients with asthma by the presence of SAD (defined as R5-R20 > 0.07) Hosmer and Lemeshow goodness of fit (GOF) test.

Table 5
Univariate and multivariate logistic regression analyses of baseline predictors of SAD.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age ≥50 y	6.06	1.39–37.98	**0.0081**	–	–	–
Sex: Female	2.45	0.66–9.09	0.1452	–	–	–
Overweight, BMI >25 kg/m^2	2.69	0.68–13.28	0.1457	–	–	–
Smoking, former or current	2.32	0.54–9.09	0.1947	–	–	–
Presence of Atopy	0.21	0.02–1.09	0.0618	–	–	–
Eosinophils count >300 mm^3	4.01	0.56–48.73	0.2200	–	–	–
FeNO >25 ppb	1.15	0.31–4.59	1.0000	–	–	–
Duration>15 y	0.92	0.23–4.09	1.0000	–	–	–
FEV<80%	0.36	0.01–29.19	0.4655	–	–	–
FEV/FVC<70%	5.97	1.00–44.65	**0.0257**	–	–	–
FEF<65%	2.25	0.43–14.11	0.2297	–	–	–
Asthma control (uncontrolled vs partially/well-controlled)	20.00	4.54–125.0	< **.0001**	–	–	–
Asthma Exacerbations	5.62	1.39–28.15	**0.0077**	–	–	–
Emergency Room visit	–			–	–	–
Hospitalization	–			–	–	–
Night awakening due to asthma, n (%)	24.95	3.27–1136.15	< **.0001**	**30.30**	**2.61–1141.00**	**0.02051**
EIB symptoms	25.12	5.05–179.8	< **.0001**	**31.18**	**4.85–365.00**	**0.00128**

IQR: interquartile range; SD: standard deviation; FEV1: Forced expiratory volume in the first second; FVC: forced vital capacity; FEF25-75: Forced Expiratory Flow Between 25% and 75%.

Odds ratios (ORs), their 95% CI and *P*-values of the Fisher's exact test. Significant *P*-values (<0.05) are represented in bold.In the multivariate logistic regression model using a backward approach only EIB symptoms and night awakening due to bronchoconstriction were retained by the model.

as that of patients in steps 3–4 of our cohort of 400 patients with persistent asthma published elsewhere [20]. Of note, patients with intermittent asthma and SAD showed significantly less well-controlled asthma than those without SAD. Overall, these findings seem to suggest that small airways are scarcely controlled in intermittent asthma, which may be the consequence of an initial inflammation not counteracted by daily ICS therapy. We believe that the coexistence of SAD and SABA-monotherapy in asthmatic patients leads to a synergistic effect, resulting in a "perfect storm", with a marked worsening of disease control and constituting a very important risk factor for severe exacerbations and increased use of SABA.

Furthermore, clinical predictors of SAD have never been investigated so far in GINA Step 1 asthma. It is worth noticing that the two independent predictors of SAD in GINA Step 1 asthma (i. e. EIB and night awakenings) are the same in patients with more severe asthma, reinforcing the hypothesis that these clinical features are shared by all asthma severities. These findings may be of help in distinguishing subjects with SAD among patients with asthma, especially when IOS cannot be performed.

SAD appears to possess the characteristics of a treatable pulmonary trait [40,41], making it certainly appealing for asthma control optimization and exacerbation rate reduction. The pharmacological management of asthma centers on inhaled medication and the peripheral region of the lung contributes significantly to asthma's clinical impact, with inflammation or resistance in the peripheral lung correlating with symptoms, asthma control, health status, dyspnea, and exacerbations [41]. Extrafine particles (i.e., those with a mass median aerodynamic diameter <2 μm) in aerosolized medicines are more able to consistently reach the peripheral lung region than nonextrafine particles [41], with resulting enhanced drug delivery to this area and improved overall lung deposition.

Therefore, our results pointed out that, given the higher prevalence of SAD in patients with intermittent asthma, the impact of as-needed extrafine ICS/formoterol formulation could be pivotal to improve IOS parameters and asthma control, potentially stopping the evolution of Step 1 asthma in more severe steps. Future studies are awaited to assess this impact in this patient subset.

Our study has some limitations. First, our cohort was relatively small. It is important to notice, however, that adult patients with GINA Step 1 asthma are often underdiagnosed and not well characterized as in our cohort. In addition, we defined asthma as diagnosed by a physician, with the potential risk of overdiagnosis. However, this is the standard criterion used for several *real-life* studies [17], and in most of the cases diagnosis was supported by standard spirometry with reversibility testing and/or methacholine challenge.

Our study has also strengths. Our analysis lies in patients with asthma with complete data on disease duration, allergic sensitization, and asthma control, which are very rarely reported in real-life studies. Furthermore, all the patients have been evaluated by the same pulmonologist expert in asthma using the same approach to disease management for all the patients. IOS, standard spirometry, and FENO were performed, following the European Respiratory Society guidelines, by the same pulmonary function technologist with the same instruments for all the patients, allowing high internal comparability and reproducibility of our results. Moreover, prevalence, impact on asthma control, and clinical predictors of SAD in asthmatic patients on GINA step 1 have never been investigated so far. Finally, these patients have been classified as intermitted by their general practitioner and not only by our pulmonary clinic, therefore the use of SABA was really on demand and not due to a scarce adherence to ICS therapy.

In conclusion, the results of our study showed significantly less well-controlled asthma, more severe exacerbations, and higher use of SABA in adult asthmatics treated with SABA monotherapy, especially in those with SAD, which supports the concerns of the GINA guidelines regarding the use of SABA as needed in step 1. In contrast with patients with partially-controlled or well-controlled asthma, SAD was present in all patients with uncontrolled asthma. In this regard, IOS should complement spirometry as part of the routine diagnostic work-up of patients with intermittent asthma. EIB symptoms and nocturnal symptoms were independent predictors of SAD in GINA Step 1 patients, helping to recognize SAD and leading to more targeted asthma management and individualized patient care in this subset of patients.

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Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Poliambulanza Brescia (protocol no. NP3364).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

CRediT authorship contribution statement

Marcello Cottini: All authors have substantially contributed to the work. **Carlo Lombardi:** Conceptualization, Validation, Investigation, Writing – original draft, Preparation, Supervision. **Pasquale Comberiati:** Conceptualization, Validation, Investigation, Writing – original draft, Preparation, Supervision. **Massimo Landi:** Validation, Data curation, Writing – review & editing. **Alvise Berti:** Validation, Writing – original draft, Preparation, Writing – review & editing. **Laura Ventura:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Global Asthma Network (GAN), The global asthma report, Available online at:, 2018 http://www.globalasthmareport.org. (Accessed 22 March 2022).
[2] C.S. Cabrera, C. Nan, N. Lindarck, M.J.H.I. Beekman, S. Arnetorp, R.J.P. van der Valk, SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting β2-agonist use in asthma, Eur. Respir. J. 55 (2) (2020 Feb 12), 1901858, https://doi.org/10.1183/13993003.01858-2019.
[3] E.D. Bateman, D.B. Price, H.C. Wang, A. Khattab, P. Schonffeldt, A. Catanzariti, R. J.P. van der Valk, M.J.H.I. Beekman, Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study, Eur. Respir. J. 59 (5) (2022 May 5), 2101402, https://doi.org/10.1183/13993003.01402-2021.
[4] R. Bhagat, V.A. Swystun, D.W. Cockcroft, Salbutamol-induced increased airway responsiveness to allergen and reduced protection versus methacholine: dose response, J. Allergy Clin. Immunol. 97 (1 Pt 1) (1996 Jan) 47–52, https://doi.org/10.1016/s0091-6749(96)70282-8.
[5] R.J. Hancox, J.O. Cowan, E.M. Flannery, G.P. Herbison, C.R. McLachlan, D. R. Taylor, Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment, Respir. Med. 94 (8) (2000 Aug) 767–771, https://doi.org/10.1053/rmed.2000.0820.
[6] D.W. Cockcroft, Inhaled beta2-agonists and airway responses to allergen, J. Allergy Clin. Immunol. 102 (5) (1998 Nov) S96–S99, https://doi.org/10.1016/s0091-6749(98)70038-7.
[7] R.E. Aldridge, R.J. Hancox, D. Robin Taylor, J.O. Cowan, M.C. Winn, C. M. Frampton, G.I. Town, Effects of terbutaline and budesonide on sputum cells and bronchial hyperresponsiveness in asthma, Am. J. Respir. Crit. Care Med. 161 (5) (2000 May) 1459–1464, https://doi.org/10.1164/ajrccm.161.5.9906052.

[8] J.K. Quint, S. Arnetorp, J.W.H. Kocks, M. Kupczyk, J. Nuevo, V. Plaza, C. Cabrera, C. Raherison-Semjen, B. Walker, E. Penz, I. Gilbert, N.L. Lugogo, R.J.P. van der Valk, SABINA north American and European study contributors. Short-acting beta-2-agonist exposure and severe asthma exacerbations: SABINA findings from Europe and north America, J. Allergy Clin. Immunol. Pract. S2213–2198 (22) (2022 Mar 29), 00285-00289.

[9] GINA report. Global strategy for asthma management and prevention, Available online at: https://ginasthma.org/. April 01, 2022).

[10] D.S. Postma, C. Brightling, S. Baldi, M. Van den Berge, L.M. Fabbri, A. Gagnatelli, A. Papi, T. Van der Molen, K.F. Rabe, S. Siddiqui, D. Singh, G. Nicolini, M. Kraft, ATLANTIS study group, Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study, Lancet Respir. Med. 7 (5) (2019 May) 402–416, https://doi.org/10.1016/S2213-2600(19)30049-9. Epub 2019 Mar 12. Erratum in: Lancet Respir Med. 2019 Sep;7 (9):e28.

[11] M. Kraft, M. Richardson, B. Hallmark, D. Billheimer, M. Van den Berge, L. M. Fabbri, T. Van der Molen, G. Nicolini, A. Papi, K.F. Rabe, D. Singh, C. Brightling, S. Siddiqui, ATLANTIS study group, The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study, Lancet Respir. Med. S2213–2600 (21) (2022 Mar 2), 00536-1.

[12] E. van der Wiel, N.H. ten Hacken, D.S. Postma, M. van den Berge, Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review, J. Allergy Clin. Immunol. 131 (3) (2013 Mar) 646–657, https://doi.org/10.1016/j.jaci.2012.12.1567.

[13] M. Contoli, J. Bousquet, L.M. Fabbri, H. Magnussen, K.F. Rabe, N.M. Siafakas, Q. Hamid, M. Kraft, The small airways and distal lung compartment in asthma and COPD: a time for reappraisal, Allergy 65 (2) (2010 Feb) 141–151, https://doi.org/10.1111/j.1398-9995.2009.02242.x.

[14] R. Chan, B. Lipworth, Forced vital capacity and low frequency reactance area measurements are associated with asthma control and exacerbations, Lung 200 (3) (2022 Jun) 301–303, https://doi.org/10.1007/s00408-022-00542-1.

[15] C.F. O'Sullivan, K. Nilsen, B. Borg, M. Ellis, P. Matsas, F. Thien, J.A. Douglass, C. Stuart-Andrews, G.G. King, G.K. Prisk, B.R. Thompson, Small airways dysfunction is associated with increased exacerbations in patients with asthma, J. Appl. Physiol. 133 (3) (1985) 629–636, https://doi.org/10.1152/japplphysiol.00103.2022, 2022 Sep. 1.

[16] M. Cottini, A. Licini, C. Lombardi, D. Bagnasco, P. Comberiati, A. Berti, Small airway dysfunction and poor asthma control: a dangerous liaison, Clin. Mol. Allergy 19 (1) (2021 May 29) 7, https://doi.org/10.1186/s12948-021-00147-8.

[17] M. Cottini, A. Licini, C. Lombardi, A. Berti, Clinical characterization and predictors of IOS-defined small-airway dysfunction in asthma, J. Allergy Clin. Immunol. Pract. 8 (3) (2020 Mar) 997–1004.e2, https://doi.org/10.1016/j.jaip.2019.10.040.

[18] M. Cottini, C. Lombardi, G. Passalacqua, D. Bagnasco, A. Berti, P. Comberiati, G. Imeri, M. Landi, E. Heffler, Small airways: the "silent zone" of 2021 GINA report? Front. Med. 9 (2022 May 23), 884679 https://doi.org/10.3389/fmed.2022.884679.

[19] M. Abdo, F. Trinkmann, A.M. Kirsten, F. Pedersen, C. Herzmann, E. von Mutius, M. V. Kopp, G. Hansen, B. Waschki, K.F. Rabe, H. Watz, T. Bahmer, Study Group, Small airway dysfunction links asthma severity with physical activity and symptom control, J. Allergy Clin. Immunol. Pract. 9 (9) (2021 Sep) 3359–3368.e1, https://doi.org/10.1016/j.jaip.2021.04.035.

[20] M. Cottini, A. Licini, C. Lombardi, A. Berti, Prevalence and features of IOS-defined small airway disease across asthma severities, Respir. Med. 176 (2021 Jan), 106243, https://doi.org/10.1016/j.rmed.2020.106243.

[21] M. Cosio, H. Ghezzo, J.C. Hogg, R. Corbin, M. Loveland, J. Dosman, P.T. Macklem, The relations between structural changes in small airways and pulmonary-function tests, N. Engl. J. Med. 298 (23) (1978 Jun 8) 1277–1281, https://doi.org/10.1056/NEJM197806082982303.

[22] J. Mead, The lung's "quiet zone, N. Engl. J. Med. 282 (23) (1970 Jun 4) 1318–1319, https://doi.org/10.1056/NEJM197006042822311.

[23] A.B. Dubois, A.W. Brody, D.H. Lewis, B.F. Burgess Jr., Oscillation mechanics of lungs and chest in man, J. Appl. Physiol. 8 (6) (1956 May) 587–594, https://doi.org/10.1152/jappl.1956.8.6.587.

[24] J.J. Cogswell, Forced oscillation technique for determination of resistance to breathing in children, Arch. Dis. Child. 48 (4) (1973 Apr) 259–266, https://doi.org/10.1136/adc.48.4.259.

[25] M. Bednarek, M. Grabicki, T. Piorunek, H. Batura-Gabryel, Current place of impulse oscillometry in the assessment of pulmonary diseases, Respir. Med. 170 (2020 Aug-Sep), 105952, https://doi.org/10.1016/j.rmed.2020.105952.

[26] D.A. Kaminsky, S.J. Simpson, K.I. Berger, P. Calverley, P.L. de Melo, R. Dandurand, R.L. Dellacà, C.S. Farah, R. Farré, G.L. Hall, I. Ioan, C.G. Irvin, D.W. Kaczka, G. G. King, H. Kurosawa, E. Lombardi, G.N. Maksym, F. Marchal, E. Oostveen, B. W. Oppenheimer, P.D. Robinson, M. van den Berge, C. Thamrin, Clinical significance and applications of oscillometry, Eur. Respir. Rev. 31 (163) (2022 Feb 9), 210208, https://doi.org/10.1183/16000617.0208-2021.

[27] M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C.P. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O.F. Pedersen, R. Pellegrino, G. Viegi, J. Wanger, ATS/ERS Task Force, Standardisation of spirometry, Eur. Respir. J. 26 (2) (2005 Aug) 319–338, https://doi.org/10.1183/09031936.05.00034805.

[28] G.G. King, J. Bates, K.I. Berger, P. Calverley, P.L. de Melo, R.L. Dellacà, R. Farré, G. L. Hall, I. Ioan, C.G. Irvin, D.W. Kaczka, D.A. Kaminsky, H. Kurosawa, E. Lombardi, G.N. Maksym, F. Marchal, B.W. Oppenheimer, S.J. Simpson, C. Thamrin, M. van den Berge, E. Oostveen, Technical standards for respiratory oscillometry, Eur. Respir. J. 55 (2) (2020 Feb 27), 1900753, https://doi.org/10.1183/13993003.00753-2019.

[29] L.M. Heinzerling, G.J. Burbach, G. Edenharter, C. Bachert, C. Bindslev-Jensen, S. Bonini, J. Bousquet, L. Bousquet-Rouanet, P.J. Bousquet, M. Bresciani, A. Bruno, P. Burney, G.W. Canonica, U. Darsow, P. Demoly, S. Durham, W.J. Fokkens, S. Giavi, M. Gjomarkaj, C. Gramiccioni, T. Haahtela, M.L. Kowalski, P. Magyar, G. Muraközi, M. Orosz, N.G. Papadopoulos, C. Röhnelt, G. Stingl, A. Todo-Bom, E. Von Mutius, A. Wiesner, S. Wöhrl, T. Zuberbier, GA(2)LEN skin test study I: GA (2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe, Allergy 64 (10) (2009 Oct) 1498–1506, https://doi.org/10.1111/j.1398-9995.2009.02093.x.

[30] American Thoracic Society; European Respiratory Society, ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005, Am. J. Respir. Crit. Care Med. 171 (8) (2005 Apr 15) 912–930, https://doi.org/10.1164/rccm.200406-710ST.

[31] S. Stanojevic, D.A. Kaminsky, M.R. Miller, B. Thompson, A. Aliverti, I. Barjaktarevic, B.G. Cooper, B. Culver, E. Derom, G.L. Hall, T.S. Hallstrand, J. D. Leuppi, N. MacIntyre, M. McCormack, M. Rosenfeld, E.R. Swenson, ERS/ATS technical standard on interpretive strategies for routine lung function tests, Eur. Respir. J. 60 (1) (2022 Jul 13), 2101499, https://doi.org/10.1183/13993003.01499-2021.

[32] H.J. Smith, P. Reinhold, M.D. Goldman, Forced oscillation technique and impulse oscillometry, in: R. Gosselink, H. Stam (Eds.), Lung Function Testing, 31, Eur Respir Mon, 2005, ISBN 978-1-904097-66-2, pp. 72–105, https://doi.org/10.1183/1025448x.ERM3105.

[33] E. Oostveen, D. MacLeod, H. Lorino, R. Farré, Z. Hantos, K. Desager, F. Marchal, ERS Task Force on Respiratory Impedance Measurements. The forced oscillation technique in clinical practice: methodology, recommendations and future developments, Eur. Respir. J. 22 (6) (2003 Dec) 1026–1041, https://doi.org/10.1183/09031936.03.00089403.

[34] B. Lipworth, A. Manoharan, W. Anderson, Unlocking the quiet zone: the small airway asthma phenotype, Lancet Respir. Med. 2 (6) (2014 Jun) 497–506, https://doi.org/10.1016/S2213-2600(14)70103-1.

[35] B.W. Oppenheimer, R.M. Goldring, M.E. Herberg, I.S. Hofer, P.A. Reyfman, S. Liautaud, W.N. Rom, J. Reibman, K.I. Berger, Distal airway function in symptomatic subjects with normal spirometry following World Trade Center dust exposure, Chest 132 (4) (2007 Oct) 1275–1282, https://doi.org/10.1378/chest.07-0913.

[36] S. Bickel, J. Popler, B. Lesnick, N. Eid, Impulse oscillometry: interpretation and practical applications, Chest 146 (3) (2014 Sep) 841–847, https://doi.org/10.1378/chest.13-1875.

[37] R.L. Dellacà, P. Santus, A. Aliverti, N. Stevenson, S. Centanni, P.T. Macklem, A. Pedotti, P.M. Calverley, Detection of expiratory flow limitation in COPD using the forced oscillation technique, Eur. Respir. J. 23 (2) (2004 Feb) 232–240, https://doi.org/10.1183/09031936.04.00046804.

[38] J. Vogel, U. Smidt, Impulse Oscillometry. Analysis of Lung Mechanics in General Practice and the Clinic, Epidemiology and Experimental Research, PMI-Verlagsgruppe, Frankfurt, 1994.

[39] M. Abdo, F. Trinkmann, A.M. Kirsten, H. Biller, F. Pedersen, B. Waschki, E. Von Mutius, M. Kopp, G. Hansen, K.F. Rabe, T. Bahmer, H. Watz, ALLIANCE study group, The relevance of small airway dysfunction in asthma with nocturnal symptoms, J. Asthma Allergy 14 (2021 Jul 13) 897–905, https://doi.org/10.2147/JAA.S313572.

[40] A. Agustí, M. Bafadhel, R. Beasley, E.H. Bel, R. Faner, P.G. Gibson, R. Louis, V. M. McDonald, P.J. Sterk, M. Thomas, C. Vogelmeier, I.D. Pavord, On behalf of all participants in the seminar. Precision medicine in airway diseases: moving to clinical practice, Eur. Respir. J. 50 (4) (2017 Oct 19), 1701655, https://doi.org/10.1183/13993003.01655-2017.

[41] O.S. Usmani, M.K. Han, D.A. Kaminsky, J. Hogg, J. Hjoberg, N. Patel, M. Hardin, C. Keen, S. Rennard, F.X. Blé, M.N. Brown, Seven pillars of small airways disease in asthma and COPD: supporting opportunities for novel therapies, Chest 160 (1) (2021 Jul) 114–134, https://doi.org/10.1016/j.chest.2021.03.047.