

Clinical significance of small airway obstruction markers in patients with asthma

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Summary

Background The role of small airway obstruction in the clinical expression of asthma is incompletely understood.

Objective We tested the hypotheses that markers of small airway obstruction are associated with (i) increased asthma severity, (ii) impaired asthma control and quality of life and (iii) frequent exacerbations.

Methods Seventy-four adults with asthma and 18 healthy control subjects underwent impulse oscillometry (IOS), multiple breath inert gas washout (MBW), body plethysmography, single-breath determination of carbon monoxide uptake and spirometry. Patients completed the six-point Asthma Control Questionnaire (ACQ-6) and standardized Asthma Quality of Life Questionnaire [AQLQ(S)]. Asthma severity was classified according to the Global Initiative for Asthma (GINA) treatment steps.

Results The putative small airway obstruction markers S_{acin} , resistance at 5 Hz minus resistance at 20 Hz (R5–R20) and reactance area (AX) were not independently associated with asthma severity, control, quality of life or exacerbations. In contrast, markers of total (R5) and mean airway resistance of large and small airways (R20) were significantly higher in the severe asthma group compared with the mild–moderate group (0.47 vs. 0.37, $P < 0.05$ for R5; 0.39 vs. 0.31, $P < 0.01$ for R20). The strongest independent contributors to ACQ-6 score were R20 and forced expiratory volume in one second (% pred.), and the strongest independent contributors to AQLQ(S) score were R20 and forced vital capacity (% pred.). A history of one or more exacerbations within the previous year was independently associated with R20.

Conclusions and Clinical Relevance Previously reported markers of small airway obstruction do not appear to be independently associated with asthma disease expression. In contrast, the IOS parameter R20, a marker of mean airway resistance of both large and small airways, appears to have independent clinical significance. These observations require confirmation in prospective longitudinal studies.

Keywords asthma, impulse oscillometry, multiple breath washout, small airway disease
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Introduction

Asthma is a common inflammatory airway disease that is estimated to affect 300 million people world-wide [1]. Inhaled corticosteroids (ICS) comprise the mainstay of asthma therapy, but deposition of most standard topical therapies is limited to the large conducting airways [2]. Persistent asthma, in which symptoms and/or airway inflammation are inadequately controlled despite topical therapy, imposes a disproportionate

burden on individual patients and society and is relatively common. Indeed, a large randomized controlled trial comparing ICS with combination ICS and long-acting β -agonist (LABA) only achieved total control of asthma at 1 year in 28% and 41% of patients, respectively [3]. The causes of persistence are not completely understood but include poor patient adherence [4, 5], inadequate inhaler technique [6] and corticosteroid resistance [7]. A further possibility is that patients with persistent asthma have pathology in the

small airways (usually defined as those with an internal diameter <2 mm) that standard topical therapy cannot reach [8].

The forced expiratory volume in one second (FEV_1) is often used to monitor asthma control and as an outcome measure in clinical trials [9]. However, FEV_1 is thought to be insensitive to small airway obstruction, and therefore, a number of putative markers of small airway obstruction have been suggested [10], as summarized in Table 1. Measures of expiratory air trapping such as the forced vital capacity (FVC) and the ratio of residual volume (RV) to total lung capacity (TLC) are often assumed to represent small airway obstruction [11], although conclusive evidence in support of this assertion is lacking [10]. Impulse oscillometry (IOS), a variant of the forced oscillation technique (FOT), allows the non-invasive assessment of lung mechanics and may provide novel insights into small airway obstruction [12]. The structural interpretation of IOS/FOT parameters has been the subject of much research, often based around computational models of lung impedance [13]. The interpretations given in Table 1 are based on our current knowledge, as previously reported [14]. In particular, the resistance at 20 Hz (R20) is thought to represent the mean level of airway resistance throughout the airway tree, encompassing both large and small airways [15]. Resistance at 5 Hz (R5) is in general

greater than at 20 Hz and represents the total airway resistance of the airway tree, arising from the series and parallel arrangement of the large and small airways. The difference between R5 and R20 (R5-R20) represents the heterogeneity of airway resistance. Finally, measures of low-frequency reactance such as the reactance at 5 Hz and reactance area (AX) are likely to reflect airway closure [16]. Multiple breath inert gas washout (MBW) is a test of gas mixing efficiency and ventilation heterogeneity within the airway tree, with lung clearance index (LCI) being a general marker of ventilation heterogeneity [17]. The indices S_{cond} and S_{acin} derived from MBW are thought to represent ventilation heterogeneity arising due to convective and diffusive-convective mechanisms, respectively [18], with convective mechanisms occurring in both the large and small conducting airways and diffusive-convective mechanisms occurring more distally in the airway tree, in the region of the acinar entrance. To summarize, while a number of physiological markers have been proposed that may provide greater insight into small airway obstruction than spirometry, these are unlikely to be completely specific to the small airways, as defined above. Moreover, it is known that the large and small airways are not independent of each other, but that they instead form a complex interacting network that may exhibit emergent properties such as catastrophic closure and reopening [19]. Therefore, the distinction between markers of large and small airway obstruction may be to a certain extent artificial.

Nevertheless, there is some evidence that the putative markers of small airway obstruction described above may relate to disease expression in patients with asthma. Bourdin *et al.* [20] found that single-breath nitrogen phase III slope correlated with Asthma Control Questionnaire (ACQ) score, although these authors did not control for possible associations between nitrogen phase III slope and FEV_1 . Farah *et al.* [21] found that changes in S_{cond} and S_{acin} correlated significantly with changes in five-point ACQ scores following treatment with high-dose ICS. The same group showed that MBW parameters could predict the symptomatic response to ICS up- or down-titration [22]. Moreover, Thompson *et al.* [23] found that S_{acin} was raised during asthma exacerbations and fell markedly as the exacerbation resolved. Shi *et al.* [24] reported that AX and R5-R20 were significantly higher in children with uncontrolled asthma compared to those with controlled asthma and that this effect was more apparent with pre-bronchodilator than post-bronchodilator measurements. Similarly, Takeda *et al.* [25] found that R20, R5-R20 and X5 were independent predictors of patient-reported outcome measures such as ACQ score and Asthma Quality of Life Questionnaire (AQLQ) score in adults with asthma. We previously showed that pre-bronchodilator R20, R5-R20

Table 1. Physiological interpretation of airway obstruction markers

Variable	Interpretation of abnormal result
Forced expiratory volume in one second (FEV_1)	Reduced ventilatory function
Forced vital capacity (FVC)	Air trapping
Ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC)	Expiratory flow limitation
Ratio of residual volume to total lung capacity (RV/TLC)	Air trapping
Ratio of alveolar volume by single-breath helium dilution to total lung capacity (VA/TLC)	Abnormal convective ventilation distribution
Lung clearance index (LCI)	Ventilation heterogeneity
S_{cond}	Conductive ventilation heterogeneity
S_{acin}	Acinar ventilation heterogeneity
Resistance at 5 Hz (R5)	Total airway resistance
Resistance at 20 Hz (R20)	Mean level of large and small airway resistance
Resistance at 5 Hz minus resistance at 20 Hz (R5-R20)	Heterogeneity of airway resistance
Reactance at 5 Hz (X5)	Airway closure
Reactance area (AX)	Airway closure

and AX were significantly higher in patients with asthma who had frequent exacerbations than in those who did not, whereas the differences were much less pronounced with post-bronchodilator measurements and only reached significance for R20 [14]. Sorkness et al. [26] found that at any given level of airflow obstruction, as measured with the FEV₁/FVC (% pred.), patients with severe asthma had more severe air trapping, as measured by reduced FVC (% pred.) and increased RV/TLC (% pred.). However, there has as yet been no study examining the contributions of each of these putative small airway obstruction markers to clinical outcomes in a single well-characterized group of adults with asthma. Moreover, with the exception of the study by Bourdin et al. [20], physiological measurements in the above studies were performed having withheld bronchodilator medications, and it is therefore possible that variations in large airway bronchial tone may have contributed to the associations that were observed. We therefore wished to specifically investigate post-bronchodilator measurements, to eliminate these variations and focus on the effects of long-term remodelling changes in the smaller airways.

In this study, we aimed to test the hypotheses that small airway obstruction markers are associated with (i) increased asthma severity, as evidenced by higher treatment requirements, (ii) impaired asthma control and quality of life and (iii) frequent exacerbations.

Materials and methods

Subjects

Seventy-four patients with asthma and 18 healthy subjects with no history of respiratory disease were recruited. All participants were over 18 years of age. Current smokers (defined as people who have smoked within the previous year) and ex-smokers with a greater than 10 pack-year smoking history were excluded from the study. Asthma was diagnosed by a specialist asthma physician in a secondary care setting according to current British Thoracic Society guidelines [27]. Asthma severity was classified according to the current Global Initiative for Asthma (GINA) treatment steps [28]. The study protocol was approved by the National Research Ethics Committee – East Midlands Leicester (approval number 08/H0406/189), and all subjects gave their written informed consent.

Study protocol

All participants attended a single visit in the stable state, not less than 6 weeks following any asthma exacerbation. Exacerbations were defined as worsening asthma symptoms for ≥ 3 days requiring additional

therapy (short burst oral prednisolone and/or antibiotics) following either primary or secondary care consultation [29]. Clinical and physiological assessment was performed in the following sequence:

- Collection of demographic and clinical details
- Completion of six-point ACQ (ACQ-6) [30] and standardized AQLQ [AQLQ(S)] [31]
- Administration of salbutamol 400 µg via metered dose inhaler and spacer
- Impulse oscillometry, using Jaeger MasterScreen Impulse Oscillometry System (Viasys Healthcare GmbH, Hoechberg, Germany) [32]
- Multiple breath washout, using sulphur hexafluoride (SF₆) wash-in method [33, 34]
- Lung volumes using body plethysmography [35]
- Single-breath determination of carbon monoxide uptake [36]
- Spirometry [37]

All physiological tests were performed in the seated position by individuals with appropriate training and accreditation. Physiological tests were performed 10 min after administration of a short-acting bronchodilator (salbutamol 400 µg). This was administered via a metered dose inhaler and spacer, with each 100 microgram actuation being inhaled in a separate inhalation to TLC, followed by a 5- to 10-s breath-hold.

Impulse oscillometry (IOS) was performed in triplicate according to standard guidelines [32]. A volume calibration was performed daily using a 3-L syringe, and the accuracy of resistance measurements was confirmed daily using a standard 0.2 kPaL⁻¹s resistance mesh. Participants wore a nose clip and supported their cheeks, while an impulse waveform was delivered to their respiratory system via a loudspeaker connected to a mouthpiece, during 60 seconds of tidal breathing. Resistance at 5 Hz (R5), resistance at 20 Hz (R20), R5-R20, reactance at 5 Hz (X5) and AX were derived from pressure and flow measurements recorded throughout the 60-second period.

Multiple breath inert gas washout (MBW) was performed in triplicate according to current guidelines [34], using the method described by Horsley et al. [33]. Volume calibration of the pneumotachometer was performed daily using a 1-L syringe. Participants wore a nose clip and breathed an air mixture containing 0.2% SF₆, while respiratory flows and exhaled breath SF₆ concentrations were monitored by an Innocor photoacoustic gas analyser (Innovision A/S, Odense, Denmark). Participants maintained a steady respiratory rate of approximately 12 breaths per minute, and a constant tidal volume of 1L, using a real-time visual display of inspired volume as a guide. Once inhaled and exhaled SF₆ concentrations had equalized, participants were switched to breathing room air during an expiration

and asked to continue breathing at the same respiratory rate and tidal volume. The test was terminated once the end-tidal concentration of SF₆ in exhaled breath reached less than 1/40th of the original concentration (0.005%) for three consecutive breaths. The parameters S_{cond} and S_{acin} [18] were calculated using custom software written with TestPoint (Measurement Computing Corporation, Norton, MA, USA).

Statistical analysis

Statistical analyses were performed using SPSS 20 (IBM Corporation, Somers, NY, USA) and Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). A *P*-value of <0.05 was taken as the threshold for statistical significance. Comparisons between or across groups were performed using Student's *t*-test or one-way analysis of variance for parametric data, the Mann–Whitney *U*-test or Kruskal–Wallis test for nonparametric data, and Fisher's exact test or the chi-squared test for proportions. Bonferroni/Dunn corrections for multiple comparisons were used as appropriate. Correlations between continuous variables were calculated using Pearson's correlation coefficient (*R*). Log-normally distributed variables were log-transformed as appropriate. Linear regression models were constructed (SPSS 20, stepwise algorithm, with probability for variable entry <0.05 and probability for variable removal >0.10) to determine the physiological determinants of ACQ and AQLQ scores. A logistic regression model (SPSS 20, forward conditional algorithm, with probability for variable entry <0.05 and probability for variable removal >0.10) was constructed to determine the physiological predictors of the exacerbation-prone phenotype, defined as having had at least one asthma exacerbation during the preceding year. The pool of variables that could potentially be entered into the linear or logistic regression models comprised FEV₁ (% pred.), FVC (% pred.), FEV₁/FVC, TLC (% pred.), RV/TLC (% pred.), alveolar volume using single-breath helium dilution (V_A), V_A/TLC, LCI, S_{cond} , S_{acin} , R5, R20, log-transformed R5–R20, X5 and log-transformed AX.

Results

Demographic, clinical and physiological data across groups are shown in Table 2. The groups did not differ significantly with respect to age, sex or body mass index. The small airway obstruction markers S_{acin} , R5–R20 and AX did not differ significantly between the asthma severity groups. However, markers of total (R5) and mean large and small airway resistance (R20) were significantly higher in the GINA 4–5 group compared with the GINA 1–3 group (0.47 vs. 0.37, *P* < 0.05 for R5; 0.39 vs. 0.31, *P* < 0.01 for R20).

Table 3 shows correlations between physiological variables and both ACQ-6 and AQLQ(S) scores, as well as FEV₁ (% pred.). ACQ-6 score correlated significantly with FEV₁ (% pred.), RV/TLC (% pred.), TLC, V_A, V_A/TLC, diffusing capacity of the lung for carbon monoxide (DL_{CO}) (% pred.), functional residual capacity from multiple breath washout (FRC_{mbw}), R5 and R20, but not with S_{acin} , log-transformed R5–R20 or log-transformed AX. The strongest correlation was with R20 (*R* = 0.369, *P* < 0.01). AQLQ(S) score correlated significantly with FEV₁ (% pred.), FVC (% pred.), RV/TLC (% pred.), TLC, V_A, V_A/TLC, DL_{CO} (% pred.), FRC_{mbw}, R5, R20 and log-transformed R5–R20, but not with S_{acin} or log-transformed AX. The strongest correlation was again with R20 (*R* = −0.430, *P* < 0.01). Linear regression models, shown in Table 4, revealed that the strongest independent contributors to ACQ-6 score were R20 and FEV₁ (% pred.), and the strongest independent contributors to AQLQ(S) score were R20 and FVC (% pred.).

Table 5 shows physiological variables between patients with and without the exacerbation-prone phenotype, defined as having had at least one asthma exacerbation within the previous year. S_{acin} , R5–R20 and AX did not differ significantly between the groups. R5 and R20 were significantly higher in the exacerbation-prone group compared with the non-exacerbation-prone group, while FVC (% pred.), TLC, V_A and DL_{CO} (% pred.) were significantly lower. A logistic regression model revealed that the only independent predictor of the exacerbation-prone phenotype was R20. In particular, a 0.1 kPa L^{−1} s increase in R20 was associated with an odds ratio of 1.86 for having the exacerbation-prone phenotype (confidence interval of odds ratio 1.12 to 3.10, *P* < 0.05).

Discussion

In this study, we investigated the relationship between clinical outcomes and a comprehensive panel of physiological measurements in a group of patients with asthma being managed in a secondary care setting, particularly focussing on measurements that are often considered to reflect small airway obstruction. We found that S_{acin} , R5–R20 and AX did not differ significantly between patients with mild–moderate asthma and those with severe asthma, nor did these parameters correlate significantly with asthma clinical outcomes. Our results on the surface appear to be discordant with those of previous studies [21–25], in which positive associations between these markers and clinical outcomes were reported. However, in these studies, bronchodilators were withheld prior to the study visits, whereas we performed all physiological tests after the administration of a bronchodilator, to eliminate the effect of large

Table 2. Demographic, clinical and physiological data across groups

	Healthy controls (<i>n</i> = 18)	Mild–moderate asthma [†] (<i>n</i> = 43)	Severe asthma [†] (<i>n</i> = 31)
Age (years)	48.3 (3.9)	57.2 (2.0)	53.8 (2.5)
Sex (% male)	50	51	39
BMI (kg/m ²)	26.8 (1.2)	27.0 (0.8)	30.0 (1.4)
Atopy (% atopic)	—	79	71
Duration of asthma (years)	—	18.7 (2.9)	25.3 (3.2)
Age of onset of asthma (years)*	—	38.4 (3.3)	28.3 (3.8)
ICS dose (BDP equivalent [mcg])****	—	547 (66)	1726 (118)
Oral prednisolone use (%)****	—	0	45
Leukotriene receptor antagonist use (%)**	—	5	35
Oral theophylline use (%)**	—	0	19
Exacerbations in past year****	—	1.0 (0.28)	3.5 (0.56)
ACQ-6 score***	—	0.99 (0.12)	1.82 (0.22)
AQLQ(S) score*	—	5.65 (0.16)	5.00 (0.23)
FEV ₁ (% pred.) ***	113.3 (4.8)	90.8 (3.4)	86.9 (4.6)
FVC (% pred.)*	117.2 (5.6)	101.1 (3.0)	105.0 (4.2)
FEV ₁ /FVC (%)***	80.7 (1.0)	73.1 (1.5)	68.4 (2.2)
TLC (L)	6.39 (0.37)	6.14 (0.21)	6.00 (0.30)
TLC (% pred.)	104.3 (3.9)	104.9 (2.5)	107.8 (3.2)
RV/TLC (% pred.)***	89.2 (3.2)	110.4 (3.1)	108.7 (2.7)
V _A (L)	5.58 (0.34)	5.07 (0.22)	4.88 (0.27)
V _A /TLC (%)**	90.3 (1.7)	82.0 (1.6)	80.8 (1.4)
DL _{co} (% pred.)	89.3 (2.9)	91.2 (2.5)	89.5 (2.9)
K _{co} (% pred.)	97.4 (2.9)	107.4 (2.7)	104.6 (3.0)
FRC _{mbw} (L)	2.52 (0.19)	2.45 (0.11)	2.39 (0.17)
LCI	7.28 (0.27)	7.79 (0.20)	7.94 (0.22)
S _{cond} (L ⁻¹)	0.033 (0.007)	0.051 (0.006)	0.038 (0.005)
S _{acin} (L ⁻¹)	0.118 (0.014)	0.175 (0.019)	0.184 (0.020)
R5 (kPa L ⁻¹ s)***	0.32 (0.03)	0.37 (0.02)	0.47 (0.03) [‡]
R20 (kPa L ⁻¹ s)***	0.29 (0.02)	0.31 (0.01)	0.39 (0.02) ^{‡‡}
R5–R20 (kPaL ⁻¹ s) [‡] *	0.03 (0.01–0.06)	0.05 (0.03–0.11)	0.05 (0.01–0.15)
X5 (kPa L ⁻¹ s)	–0.10 (0.01)	–0.13 (0.01)	–0.15 (0.02)
AX (kPa L ⁻¹) [‡] *	0.23 (0.16–0.54)	0.41 (0.24–0.66)	0.47 (0.23–1.27)

BMI, body mass index; ICS, inhaled corticosteroid; BDP, beclometasone dipropionate; ACQ-6, Six-point Asthma Control Questionnaire; AQLQ(S), standardized Asthma Quality of Life Questionnaire; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; V_A, alveolar volume (single-breath helium dilution); DL_{co}, diffusing capacity of the lung for carbon monoxide; K_{co}, carbon monoxide transfer coefficient; FRC_{mbw}, functional residual capacity from multiple breath washout; LCI, lung clearance index; R5/R20, resistance at 5 Hz/20 Hz; R5–R20, resistance at 5 Hz minus resistance at 20 Hz; X5, reactance at 5 Hz; AX, reactance area.

[†]Mild–moderate asthma refers to Global Initiative for Asthma (GINA) treatment steps 1–3; Severe asthma refers to GINA treatment steps 4–5.

Data expressed as mean (standard error), [‡]median (interquartile range) or proportions. Groups compared using Student's t-test or one-way analysis of variance for parametric data, Kruskal–Wallis test for nonparametric data and Fisher's exact test or the chi-squared test for proportions. Bonferroni/Dunn corrections for multiple comparisons used as appropriate. Significant differences across groups denoted *(*P* < 0.05), **(*P* < 0.01), ***(*P* < 0.001) or ****(*P* < 0.0001). Significant differences between GINA 1–3 and GINA 4–5 groups denoted [‡](*P* < 0.05) or ^{‡‡}(*P* < 0.01).

airway smooth muscle tone and thus accentuate as much as possible the effects of the distal small airways. It is therefore possible that the associations that were observed in previous studies were at least partly related to the effect of proximal airway tone impacting upon

the heterogeneity of distal airway calibre. Indeed, both we [14] and others [24] have previously found that pre-bronchodilator physiological measurements correlate more strongly with asthma outcomes than post-bronchodilator measurements.

Table 3. Correlations between clinical outcome measures and physiological variables

	ACQ-6 score	AQLQ(S) score	FEV ₁ (% pred.)
FEV ₁ (% pred.)	-0.285*	0.289*	—
FVC (% pred.)	-0.230	0.299*	0.835**
FEV ₁ /FVC	-0.166	0.100	0.657**
TLC	-0.252*	0.254*	0.100
TLC (% pred.)	-0.118	0.154	0.416**
RV/TLC (% pred.)	0.268*	-0.322**	-0.573**
V _A	-0.300*	0.322**	0.214
V _A /TLC	-0.248*	0.274*	0.358**
DLco (% pred.)	-0.286*	0.313**	0.348**
Kco (% pred.)	-0.084	0.019	-0.216
FRC _{mbw}	-0.240*	0.243*	0.106
LCI	0.151	-0.202	-0.406**
S _{cond}	0.139	0.025	-0.196
S _{acin}	0.160	-0.168	-0.200
R5	0.341**	-0.405**	-0.340**
R20	0.369**	-0.430**	-0.169
log R5-R20	0.221	-0.250*	-0.379**
X5	-0.070	0.091	0.402**
log AX	0.173	-0.202	-0.492**

ACQ-6, Six-point Asthma Control Questionnaire; AQLQ(S), standardized Asthma Quality of Life Questionnaire; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; V_A, alveolar volume (single-breath helium dilution); DLco, diffusing capacity of the lung for carbon monoxide; Kco, carbon monoxide transfer coefficient; FRC_{mbw}, functional residual capacity from multiple breath washout; LCI, lung clearance index; R5/R20, resistance at 5 Hz/20 Hz; R5-R20, resistance at 5 Hz minus resistance at 20 Hz; X5, reactance at 5 Hz; AX, reactance area. Pearson's correlation coefficients are shown. Significant correlations are indicated *($P < 0.05$) or **($P < 0.01$).

An unexpected finding of our study was the striking relationship between the IOS parameter R20 and a number of clinically important outcome measures such as asthma control, quality of life and exacerbations. Moreover, in multivariate linear regression analyses, the contribution of R20 was additive to that of traditional spirometric outcome measures such as FEV₁ and FVC, suggesting that it may represent a distinct facet of asthma disease expression. Although the structural correlates of IOS parameters have not yet been defined, R20 is thought to reflect the mean level of airway resistance, including both the large and small airways,

whereas R5-R20 represents the heterogeneity of airway resistance. Computational models and ex vivo prototypic models of lung impedance based upon realistic airway geometry may shed further light on this area in the near future [38].

The association observed in this study between absolute lung volumes and asthma exacerbations is intriguing and, to our knowledge, has not been previously reported. In particular, we found that patients with a history of one or more exacerbations within the previous year had significantly lower TLC and V_A than those without a history of recent exacerbations. This was contributed to partly by a lower TLC (% pred.) in the exacerbation-prone group, although this did not reach statistical significance, and partly by a greater proportion of females in the exacerbation-prone group, although this also did not reach statistical significance. The reduced DLco (% pred.) seen in the exacerbation-prone group was driven primarily by the lower absolute lung volumes, because neither Kco (% pred.) nor the V_A/TLC ratio differed significantly between the two groups. These observations suggest that a preserved TLC may have a protective effect against exacerbations of asthma, a possibility that merits further investigation.

We found that physiological variables explained approximately one-fifth of the variance of ACQ-6 and AQLQ(S) scores. The lack of a strong association between physiological variables and patient-reported outcome measures in patients with asthma has been previously documented [39, 40], although the causes of this are poorly understood. One possible explanation is that patients with asthma become accustomed to a certain level of disease control, thus regarding this as their normal baseline state. Therefore, patient-reported measures of asthma control or quality of life may be related more strongly to changes in physiological variables, rather than to their absolute values. Moreover, it is likely that subjective measures of asthma control are influenced by a large number of factors other than the function of the lower airways, including obesity [41], deconditioning [42], dysfunctional breathing [43, 44], vocal cord dysfunction [44] and psychological factors [45].

Our study was limited by its cross-sectional design, and a number of important questions remain about the

Table 4. Linear regression models assessing the contributions of physiological variables to ACQ-6 and AQLQ(S) scores

Dependent variable	Constant term	Independent variables	Unstandardized coefficient (B)	Standardized coefficient (β)	P-value	Model R ²
ACQ-6 score	1.129	R20 (kPa L ⁻¹ s)	3.276	0.330	0.005	0.187
		FEV ₁ (% pred.)	-0.010	-0.229	0.046	
AQLQ(S) score	5.459	R20 (kPa L ⁻¹ s)	-4.355	-0.398	< 0.0005	0.229
		FVC (% pred.)	0.014	0.248	0.026	

ACQ-6, Six-point Asthma Control Questionnaire; AQLQ(S), standardized Asthma Quality of Life Questionnaire; R20, resistance at 20 Hz; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

Table 5. Demographic and physiological variables in exacerbation-prone and non-exacerbation-prone patients with asthma

	Non-exacerbation prone [†] (n = 34)	Exacerbation prone [†] (n = 40)
Age (years)*	59.9 (1.5)	52.2 (2.5)
Sex (% male)	59	35
BMI (kg/m ²)	27.3 (0.9)	29.0 (1.2)
FEV ₁ (% pred.)	94.0 (4.5)	85.1 (3.3)
FVC (% pred.)*	108.2 (3.7)	97.9 (3.1)
FEV ₁ /FVC (%)	70.1 (2.0)	72.1 (1.7)
TLC (L)**	6.59 (0.23)	5.66 (0.24)
TLC (% pred.)	109.8 (3.3)	103.1 (2.3)
RV/TLC (% pred.)	106.0 (3.4)	115.6 (3.9)
V _A (L)**	5.48 (0.23)	4.58 (0.23)
V _A /TLC (%)	82.8 (1.6)	80.3 (1.4)
DLco (% pred.)**	96.1 (2.9)	85.8 (2.2)
Kco (% pred.)	108.4 (2.9)	104.4 (2.7)
FRC _{mbw} (L)	2.58 (0.13)	2.30 (0.13)
LCI	8.01 (0.24)	7.71 (0.19)
S _{cond} (L ⁻¹)	0.052 (0.007)	0.052 (0.009)
S _{acin} (L ⁻¹)	0.197 (0.023)	0.170 (0.018)
R5 (kPa L ⁻¹ s)*	0.37 (0.03)	0.45 (0.02)
R20 (kPa L ⁻¹ s)**	0.31 (0.02)	0.37 (0.02)
R5-R20 (kPa L ⁻¹ s) [‡]	0.04 (0.02–0.09)	0.06 (0.03–0.13)
X5 (kPa L ⁻¹ s)	–0.14 (0.02)	–0.13 (0.01)
AX (kPa L ⁻¹) [‡]	0.33 (0.20–0.71)	0.51 (0.29–1.24)

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; V_A, alveolar volume (single-breath helium dilution); DLco, diffusing capacity of the lung for carbon monoxide; Kco, carbon monoxide transfer coefficient; FRC_{mbw}, functional residual capacity from multiple breath washout; LCI, lung clearance index; R5/R20, resistance at 5 Hz/20 Hz; R5-R20, resistance at 5 Hz minus resistance at 20 Hz; X5, reactance at 5 Hz; AX, reactance area.

[†]Exacerbation prone defined as having had at least one asthma exacerbation in the previous year.

Data expressed as mean (standard error), [‡]median (interquartile range) or proportions. Groups compared using Student's t-test for parametric data, [‡]Mann-Whitney U-test for nonparametric data or Fischer's exact test for proportions. Significant differences between groups denoted *(P < 0.05), ***(P < 0.01), ****(P < 0.001) or *****(P < 0.0001).

role of small airway obstruction in the clinical expression of asthma. Most notably, it is not known whether small airway obstruction affects the long-term outcome of patients with asthma, and longitudinal studies are required to address this issue. A further limitation of the study is that exacerbation frequency was assessed retrospectively, and therefore, it is possible that the associations we observed relate to the after-effects of a recent exacerbation, rather than being predictive of future exacerbations. Prospective studies examining the physiological determinants of exacerbation risk are required to resolve this issue.

In conclusion, we have investigated the clinical correlates of a broad panel of physiological parameters in a well-characterized group of patients with asthma.

Measurements that have traditionally been considered to represent small airway obstruction, such as S_{acin}, R5-R20 and AX, do not appear to be associated with impaired asthma control or quality of life cross-sectionally, although the long-term significance of these parameters requires further investigation. In contrast, the IOS parameter R20 is strongly and independently associated with adverse outcome, suggesting that asthma clinical disease expression is associated with obstruction of both the large and small airways. Further studies are required to confirm this novel finding and to investigate its clinical significance.

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Author contributions

SG performed physiological tests, conducted statistical analysis of the data and wrote the manuscript; SN performed physiological tests; DD recruited subjects; SC performed physiological tests; AS recruited subjects and performed physiological tests; PG provided expertise and the analysis software for multiple breath washout; CEB, PB, RC, RK and HP contributed to study conception and design and critically reviewed the manuscript; SS conceived and supervised the study, analysed the data and critically reviewed the manuscript.

Conflict of interests

RC is an employee of Chiesi UK Ltd.; RK and HP are shareholders, and were employees, of Hoffmann–La Roche. CEB has received grant funding from Roche-Genentech, Novartis, AZ-MedImmune, and GSK, and consultancy from Hoffmann–La Roche, AZ, GSK, Novartis and Merck. SS has received research grants from Chiesi to study small airway microstructure and has received lecturing fees from Chiesi. SG has received funding for travel to scientific meetings from GSK. SN, DD, SC, AS, PB and PG have no conflict of interests to declare.

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