Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Peripheral Airway Obstruction in Association with Symptoms and Quality of Life in Asthma

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Introduction: Forced Oscillation Technique (FOT) is increasingly used to measure obstruction in the airways; however, the association between airway obstruction and the actual symptom burden in asthma is not known. Therefore, we aimed to investigate central and peripheral airway obstruction, measured by FOT, in association to symptoms and quality of life in asthma.

Methods: 319 asthma patients were recruited and answered questionnaires focusing on symptoms (ACT, ACQ, Nijmegen, HADS and SNOT-22) and quality of life (MiniAQLQ and MiniRQLQ) and performed FOT measurements estimating airway resistance (R5: total resistance, R19: central resistance, R5-R19: peripheral resistance) and reactance (X5) during inspiration and expiration.

Results: Asthma groups classified based on ACT score cut-off points at 16, 20, and 25 showed higher R5, R5-R19, and lower X5 with increasing symptoms, which was not evident when applying a cut-off of only 20. ACQ-5 cut-offs at 0.75 and 1.5 captured differences in R5 and X5, whereas a Nijmegen cut-off of 23 showed differences in R5 and R19. The total scores from most questionnaires (except for the HADS and SNOT-22) correlated with many of the FOT results, but there were different patterns of correlation between airway obstruction and symptoms in uncontrolled and controlled asthma. Additionally, specific questions were associated with airway obstruction.

Conclusion: The increasing symptoms in patients with asthma assessed using questionnaires correlated well with predominantly increasing peripheral airway obstruction. A correlation also exists with the Nijmegen score, which is not specific to asthma. The cut-off points used to define asthma control may capture peripheral airway dysfunction.

Keywords: asthma, symptom, quality of life, airway obstruction

Background

Defining disease control and severity grades in asthma, a truly heterogeneous disease, remains a persistent challenge for clinicians. The most recent GINA guidelines focus extensively on the evaluation of asthma control and how both physician and patient perspectives should be taken into consideration.[1] In the attempt to assess asthma and achieve symptom control, standardised methods are used when initially diagnosing asthmaand during follow-ups.

Objective methods, such as spirometry, which is relatively easy to perform, are combined with subjective methods, such as patient-reported outcomes when using standard validated questionnaires, in order to obtain as much information as possible. Spirometry is, however, known to be inefficient when examining patients with small airway dysfunction.[2] Also, the evaluation of asthma control can be misleading if conclusions are based only on patient-reported outcomes, even though the questionnaires are standardised and validated. Apart from symptoms, even quality of life (QoL) in asthma patients is commonly assessed using standardised validated questionnaires, but neither this method is optimal.[3] The extent to which asthma, a chronic disease, affects the quality of life remains difficult to capture. Most QoL questionnaires contain a long symptom list[4] that is thought to be representative for the symptoms that asthma patients experience and may affect their life quality. Even so, a certain problem emerges. In chronic respiratory diseases such as asthma, it is commonly observed that symptoms are underestimated by the patients, for example the degree of

Received: 21 September 2024
Accepted: 13 February 2025
Published: 5 April 2025

dyspnoea.[5,6] The disease is progressing over the years, and most patients adjust their lifestyle and exercise habits, mainly by avoiding strenuous physical activity. Furthermore, the questionnaires are not adjusted for different grades of disease severity.[7] Under the umbrella diagnosis of asthma, central and peripheral areas of the airways are affected, resulting in a wide range of symptoms that are present neither in all types of asthma nor grades of disease severity.[8] When conclusions are based only on patient-reported outcomes, a lack to identify the various symptoms could potentially lead to poorer control of the disease and inaccurate severity grading. Another element that is usually overlooked, when evaluating disease control and severity grade, is the obstruction of the peripheral airways. In an attempt for a detailed assessment of the airways obstruction, and indirectly of disease severity, the conventional spirometry, that can mainly measure the central airway obstruction,[9,10] has been frequently evaluated alongside with other measurement techniques.[11]

Forced Oscillation Technique (FOT) is a method easy to perform and increasingly used to measure obstruction in the peripheral airways.[12] The respiratory oscillation parameters evaluated in previous studies were resistance (R) at 5 hz and 20 hz, representing the total and central airway resistance, respectively, and reactance (X) at 5 hz.

The role of the peripheral airway obstruction in asthma is complex and as researchers in the field come across challenges, different terms emerge, in order to describe in detail various observations, such as expiratory vs inspiratory flow limitation and air-trapping. During expiration, intrathoracic pressure compresses the airways; therefore, expiratory resistance is increased in comparison to inspiration. In previous studies, peripheral airway resistance, presented as the difference between the total airway resistance and central airway resistance (R5-R19), correlated less with symptoms and quality of life in patients with asthma than in those with COPD. However, most studies have investigated resistance and reactance as a whole, rather than separately during inspiration and expiration.[13,14] The difference between expiratory and inspiratory resistance and reactance can be used as an estimate of expiratory flow limitation and has been shown to correlate with air trapping.[15] Air trapping is a condition noticed during expiration that represents a significant amount of air remaining in the lungs before the next inspiration. It has been studied mostly in patients with COPD and is directly associated with the degree of dyspnoea,[16] it is presumably present in all obstructive respiratory diseases. Expiratory flow limitation is believed to be associated with symptoms, exercise performance, and exacerbations in COPD but requires further investigation in asthma.

Aim

Therefore, we aimed to investigate how inspiratory and expiratory resistance and reactance of obstruction in the central and peripheral airways, measured using the FOT, were associated with various symptoms and quality of life.

Methods

Study Participants

Data was collected within a previous study,[17] which was a cross-sectional study of real-life patients. A total of 319 patients with asthma, previously diagnosed by a physician and with confirmation of diagnosis during the study, were recruited to perform the measurement of airway obstruction by FOT (Table 1). The participants were either newly referred patients, patients at regular controls at the primary care clinic, or subjects recruited through web-based advertising.

The exclusion criteria were malignant (lung) disease or any other lung disease of clinical significance, pregnancy, lower airway infection within six weeks, and exacerbation or infection requiring prednisolone or antibiotics within six weeks.

All subjects signed written informed consent, and the study was approved by the Regional Ethical Review Board in Lund, Sweden (2016/1069) and follows the Declaration of Helsinki.

Study Design

The patients completed standardised and validated questionnaires regarding their symptoms and quality of life. All patients underwent lung function tests including spirometry and Forced Oscillation Technique measurements.

Table 1 Patient Characteristics

	All Patients (n=319)	Patients with ACT <20 (n=107)	Patients with ACT ≥20 (n=212)	p-value
Age, years	49 (18–80)	50 (18–80)	49 (18–79)	0.105
Sex (female/male), %	53/47	62/38	49/51	**0.033**
BMI, kg/m^2	25.3 (16.6–42.0)	26.5 (18.0–38.3)	25.1 (16.6–42.0)	**0.007**
Smoking status (%)				0.67
Never-smokers	64.9	65.4	64.6	
Former smokers	32	31.8	32.1	
Current smokers	3.1	2.8	3.3	
Positive Phadiatop, %	59.6	52.3	63.2	0.090
FEV_1, L	3.06 (0.89–5.64)	2.77 (0.89–5.64)	3.16 (1.18–5.59)	**0.012**
FEV_1, % of predicted	87 (36–123)	86.00 (38–120)	89 (36–123)	0.084
FVC, L	3.93 (1.59–7.14)	3.71 (1.59–7.13)	4.10 (1.78–7.14)	**0.009**
FVC, % of predicted	91 (47–122)	89 (47–122)	93 (52–119)	**0.012**
R5, % of predicted	92 (72–114)	92 (73–111)	92 (72–118)	0.66
R19, % of predicted	92 (72–112)	95 (74–112)	88 (71–112)	0.40
X5, % of predicted	86 (58–120)	88 (61–119)	78 (54–123)	0.13
ACT, score	21(18–24)	17 (13–18)	23 (21–24.75)	**<0.001**
ACQ-5, score	4 (2–8)	10 (7–14)	3 (1–5)	**<0.001**
MiniAQLQ, score	89 (77–96)	74 (67–83)	93 (87–100)	**<0.001**
Nijmegen, score	12 (6–18)	18 (12–27)	9 (4–15)	**<0.001**
HADS, score	5 (2–9)	7 (4–12)	4 (2–7)	**<0.001**
SNOT-22, score	17 (7–28)	25 (7–36)	16 (7–25)	**<0.001**
MiniRQLQ, score	16 (7–26)	25 (16–37)	13 (6–21)	**<0.001**

Notes: Data is shown as median values (IQR) or number (in %) where indicated. Significant p-values are presented in bold. P-values present comparison between patients with ACT<20 versus ACT≥20.

Abbreviations: ACT, asthma control test; ACQ, asthma control questionnaire; BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; MiniAQLQ, mini version of Asthma Quality of Life Questionnaire; MiniRQLR, mini version of Rhinoconjunctivitis Quality of Life Questionnaire; Nijmegen, questionnaire that is used to screen patients with dysfunctional breathing such as hyperventilation syndrome (a score of over 23 out of 64 suggest a positive diagnosis of hyperventilation syndrome); R5, Resistance at 5Hz; R19, Resistance at 19Hz; SNOT-22, Sino-nasal outcome test; X5, Reactance at 5 hz.

Questionnaires

Symptoms

The Asthma Control Test (ACT)[18] and the Asthma Control Questionnaire (ACQ-5)[19] were used to evaluate asthma-related symptoms. The ACT covers symptoms during the last four weeks and includes five questions scoring 1–5 where 1 indicates the most symptoms (maximum score=25, which indicates no symptoms and defines a fully controlled disease). An ACT score ≥20 indicates controlled disease, while an ACT score <20 indicates uncontrolled asthma (ACT score <16 indicates poorly controlled disease).[18]

The ACQ asks about symptoms in the last week and is numerically reversed in comparison to the ACT. In this study, five questions in the ACQ were used (ACQ-5) with a scoring of 0–6 where 6 means most symptoms (maximum number=30, and thereafter divided by the number of questions giving a maximum score of 6). An ACQ score <0.75 indicates well-controlled asthma, and >1.5 indicates poorly controlled asthma, respectively.

The Hospital Anxiety and Depression Scale (HADS)[20] was used to determine the levels of anxiety and depression experienced by patients. The HADS includes 14 questions scoring 0–3 where 3 indicates the highest anxiety/depression (maximum score=42). The Nijmegen questionnaire[21,22] was used to screen patients with dysfunctional breathing, such as hyperventilation syndrome, and included 16 questions, each scoring 0–4, where 4 indicates most symptoms (maximum score=64). Sino-Nasal Outcome Test 22 (SNOT-22)[23] is a validated patient-reported outcome measure for chronic rhinosinusitis during the last two weeks, and includes 22 questions with scoring 0–5, where 5 indicates most symptoms (maximum score=110).

Quality of Life

The mini version of the Asthma Quality of Life Questionnaire (MiniAQLQ)[24] includes 15 questions about asthma symptoms in the last two weeks, scoring 1–7 where 7 is the most common symptom (maximum score=105). The mini-version of the Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) includes 14 questions about symptoms from the nose and eyes during the last week, scoring 0–6 where 6 indicates most symptoms (maximum score=84).

Spirometry

Forced expiratory volume of the first second (FEV1) and forced vital capacity (FVC) were measured using a spirometer (Medisoft, Sorinnes, Belgium), spirometry maneuvers were performed according to the standards recommended by the American Thoracic Society/European Thoracic Society,[25] and reference equations of normal distribution from Quanjer et al[26] were used.

Forced Oscillation Technique (FOT)

FOT is an increasingly used method,[27] with low cost and ease of performance, and is used to measure the mechanics of the respiratory system by measuring the respiratory resistance (R) and reactance (X) during tidal breathing while wearing a nose clip. Resistance and reactance can be measured separately during inspiration and expiration, and the difference between them can be used as a measure of expiratory flow limitation.[28] In this study, the FOT device Resmon Pro Full (Restech srl, Milan, Italy) was used to measure the resistance at 5 hz (R5) and 19 hz (R19) and reactance at 5 hz (X5) during inspiration and expiration as well as the total measure. The reference equations from Oostveen et al.[29]

Statistics and Data Analyses

Standard validated questionnaires (ACT, ACQ, MiniAQLQ, MiniRQLQ, HADS, Nijmegen and SNOT-22) were evaluated as total scores, and some questionnaires were evaluated as separate questions (ACT, ACQ and Nijmegen). A correlation analysis was performed, using Spearman rank test, between the questionnaires and the forced oscillation technique (FOT) measurements of resistance (R5 and R19) and reactance (X5) during inspiration, expiration or as a total. Linear regression analyses were performed after adjusting for age and sex. The patients were divided into two groups based on ACT: controlled disease (ACT≥20), uncontrolled disease (ACT<20), and Nijmegen (≤ or >23), and analysed using the Mann–Whitney *U*-test. When investigating more than two groups, the Kruskal–Wallis test was used with Dunn's post hoc test for multiple comparisons between separate groups.

Results

Of the 319 patients with asthma, 212 had controlled disease (ACT ≥ 20), of which 53 had totally controlled disease (ACT=25). The remaining 107 patients had uncontrolled disease (ACT<20), of whom 29 had poorly controlled disease (ACT<16) (Figure 1A).

As expected, patients with uncontrolled asthma, as defined by the ACT score (<20), had more symptoms and worse quality of life than those with controlled asthma (Table 1).

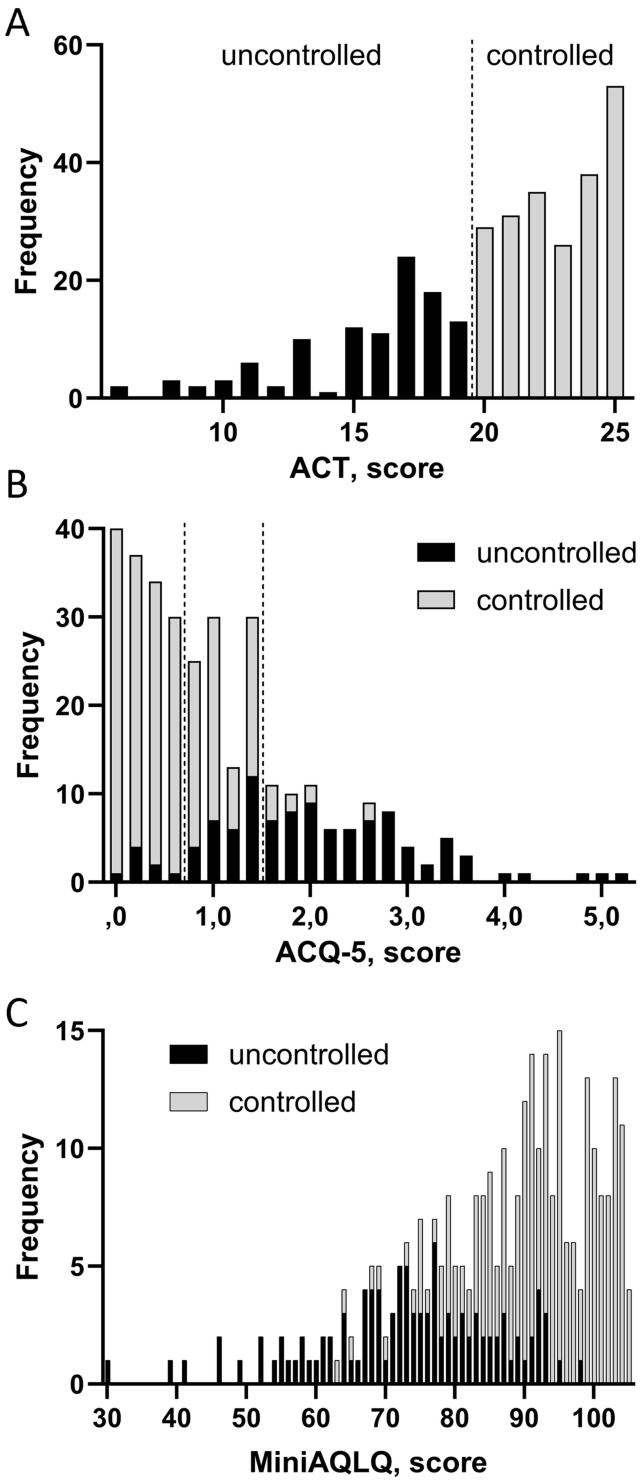

Figure 1 Frequency distribution of number of subjects with asthma with the separate scores from ACT (**A**), ACQ-5 (**B**) and MiniAQLQ (**C**) grouped according to uncontrolled (black bars) or controlled (grey bars) asthma based on ACT score < or ≥20, respectively. Dotted line separates uncontrolled and controlled disease (**A**), and well controlled, partly controlled and poorly controlled based on ACQ (**B**).

When investigating the ACQ-5 (which has a reversed scoring system compared to ACT), only 141 patients had a total score <0.75, indicating well-controlled asthma; 98 patients had an ACQ-score between 0.75–1.5 indicating partly controlled asthma; and 80 patients had a total score >1.50, indicating poorly controlled asthma. As expected, there was high agreement between ACT and ACQ-5 (Figure 1B).

https://doi.org/10.2147/JAA.S497218

In addition, the distribution of the MiniAQLQ scores showed high agreement with ACT (Figure 1C), with lower MiniAQLQ scores in patients with uncontrolled asthma. The distribution of the scores from the other questionnaires is shown in Figure 2 (HADS and Nijmegen) and Supplemental Figure 1 (MiniRQLQ and SNOT-22).

None of the scores in the respective questionnaires showed a normal distribution, either in the total score or in separate questions.

Correlation Between Scores From the Different Questionnaires

Scores from all questionnaires demonstrated strong correlations when the patient group was analysed as a whole (Supplemental Table 1). The ACT, ACQ, and MiniAQLQ scores were strongly correlated with each other. The Nijmegen score and MiniRQLQ showed moderate correlations with asthma symptoms, whereas HADS, Nijmegen, and SNOT-22 only showed weak correlations with asthma symptoms. In subjects with controlled asthma, these correlations were still observed (Supplementary Table 1, lower part), but in subjects with uncontrolled disease, there were only correlations within asthma symptoms, Nijmegen, and quality of life (Supplementary Table 1, middle part).

Subsequently, there were differences between the groups with controlled and uncontrolled asthma (according to ACT < or ≥20) and the total scores of all the other questionnaires (Table 1).

Correlation Between FEV1 and FVC and the Questionnaire Scores

When examining the whole group of patients, regardless of disease control, both FEV1 and FVC correlated with ACT, ACQ, MiniAQLQ, and Nijmegen (Supplemental Table 2). FEV1 and FVC (% of predicted values) also correlated with

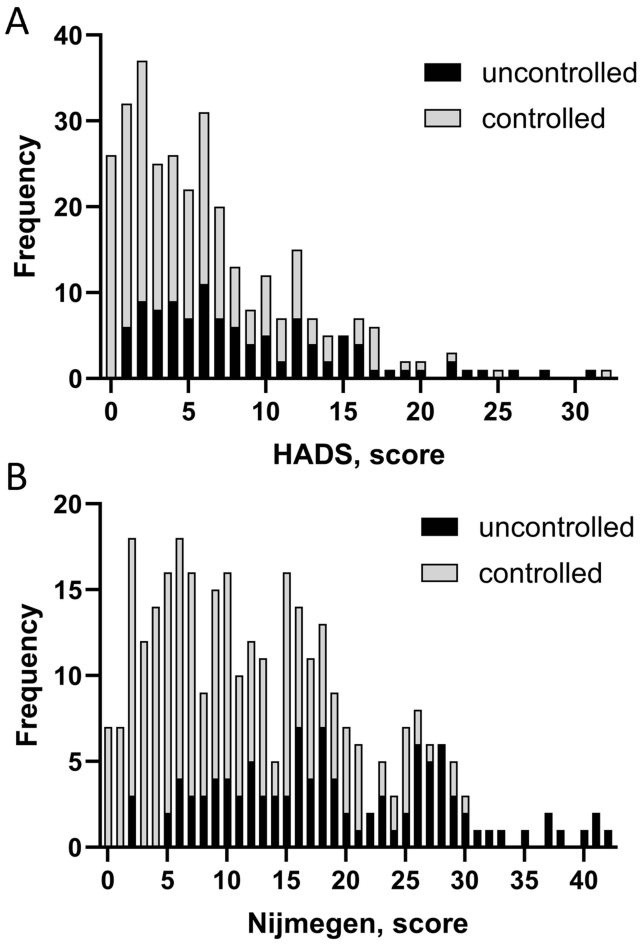

Figure 2 Frequency distribution of number of subjects with asthma with the separate scores from HADS (**A**) and Nijmegen (**B**) scores grouped according to uncontrolled (black bars) or controlled (grey bars) asthma based on ACT score < or ≥20.

ACQ and MiniAQLQ but less with ACT. In patients with uncontrolled asthma (ACT<20), neither FVC nor FEV1 (and neither as % of predicted values) correlated with ACT. Correlations between FVC and ACQ, MiniAQLQ, and Nijmegen were still present, while FVC as a percentage of predicted values correlated only with ACQ. In patients with controlled asthma (ACT≥20), neither FVC nor FEV1 correlated with ACT, but FVC correlated with ACQ, and more to MiniAQLQ, and Nijmegen.

ACT and ACQ Score in Relation to Airway Resistance and Reactance

An ACT score cut-off of 20, resulting in two patient groups with controlled and uncontrolled disease, revealed only a difference in expiratory peripheral resistance (R5-R19exp) and reactance (X5exp) between the groups (Supplemental Figure 2). However, when further dividing the subjects into four patient groups (ACT score = 25, 20–24, 16–19 and <16), there were clear differences in total and peripheral resistance, as well as reactance, among the groups (Figure 3). In contrast, resistance in the central airway was not similarly associated with symptom severity.

ACQ scores can be used to define the three groups (<0.75, 0.75–1.5 and >1.5), and R5 and X5 were overall higher with increasing symptoms, specifically in expiratory measures (Figure 4).

Correlations Between Airway Resistance and Reactance and Asthma Symptoms

In conjunction with the higher total resistance (R5) in the groups with the most asthma symptoms presented above, R5 (both insp and exp) correlated with the total ACT, ACQ5, Nijmegen, MiniAQLQ, and MiniRQLQ scores (Table 2). R5 was also correlated with scores from separate questions (q), such as ACTq1 (daily activities) and ACTq2 (shortness of breath), but not ACTq3 (night symptoms). ACTq4 (rescue medication) and ACTq5 (asthma control) correlated only with expiratory R5. In addition, R5 was correlated with scores from separate ACQ questions such as ACQq3 (limited activity) and ACQq4 (shortness of breath).

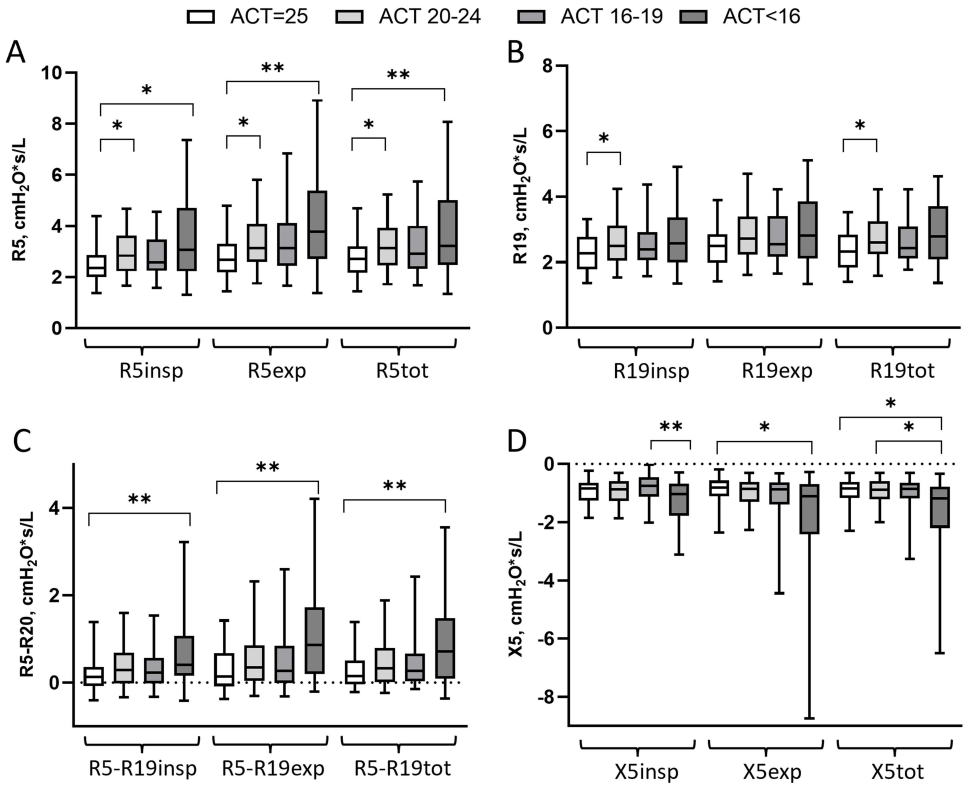

Figure 3 Box-plots of R5 (**A**), R19 (**B**), R5-R19 (**C**) and X5 (**D**) in groups of asthma separated according to ACT=25, ACT=20-24, ACT=16-19 and ACT=<16. *=p<0.05, **=p<0.01 from statistical analyses using Kruskal–Wallis test for overall comparisons followed by Dunn's test for multiple comparisons between separate groups.
Abbreviations: insp, inspiratory; exp, expiratory; tot, total.

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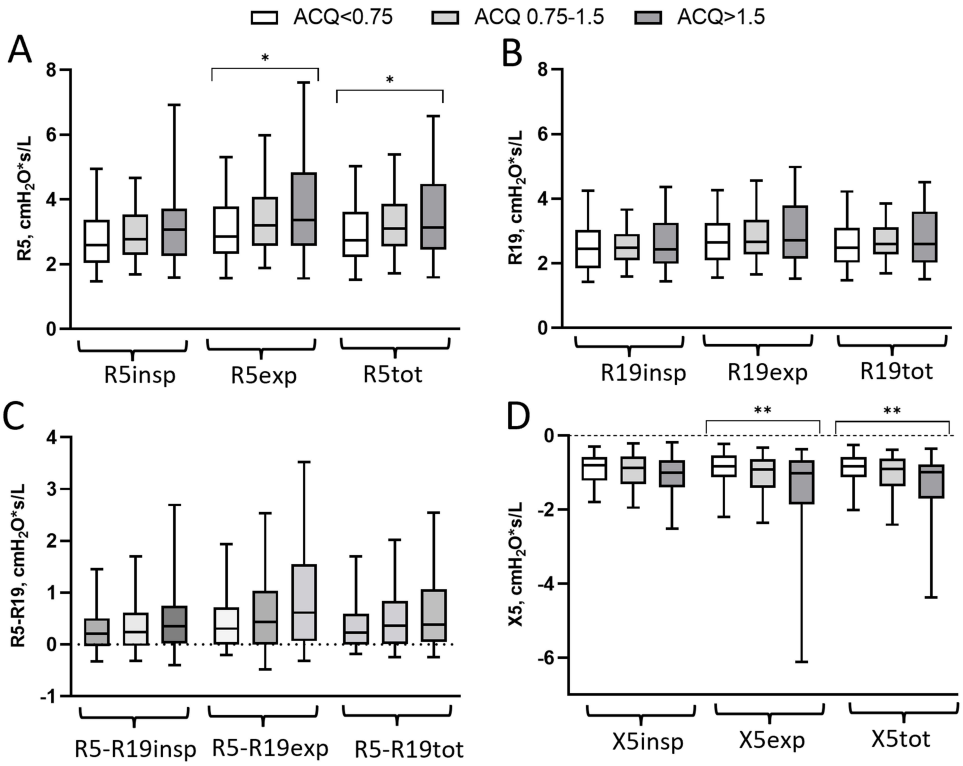

Figure 4 Box-plots of R5 (**A**), R19 (**B**), R5-R19 (**C**) and X5 (**D**) in groups of asthma separated according to ACQ<0.75, ACQ=0.75–1.5 and ACQ>1.5. *=p<0.05, **=p<0.01 from statistical analyses using Kruskal–Wallis test for overall comparisons.
Abbreviations: insp, inspiratory; exp, expiratory; tot, total.

Most of these correlations were also apparent in the controlled asthma group (ACT≥20) but not in those with uncontrolled asthma (ACT<20, Supplemental Table 3a and b).

Central resistance (R19) only weakly correlated with the total score of ACT, Nijmegen and MiniRQLQ, and only weakly correlated with ACTq2 (shortness of breath) as separate questions (Table 2). R19 correlated with Nijmegen, but in controlled and uncontrolled asthma, and with total ACT, ACTq1 (limited activity), and ACTq2 (shortness of breath) in controlled asthma (Supplemental Table 3a and b).

Peripheral resistance (R5-R19) correlated with the total score of ACT, ACQ and MiniAQLQ and separate questions, such as ACTq1 (limited activity), ACQq1 (night symptoms), and ACQq5 (wheeze) in all subjects with asthma. No

Table 2 Correlations Between Questionnaire Score and Forced Oscillation Technique Measurements in All Patients (n=319)

		$R5_{in}$	$R5_{exp}$	$R5_{tot}$	$R19_{in}$	$R19_{exp}$	$R19_{tot}$	$R5\text{-}R19_{in}$	$R5\text{-}R19_{ex}$	$R5\text{-}R19_{tot}$	$X5_{in}$	$X5_{exp}$	$X5_{tot}$
ACTsum	p	**0.008**	**0.002**	**0.004**	**0.038**	**0.047**	**0.045**	**0.037**	**0.011**	0.82	0.788	**0.009**	**0.042**
	r	−0.149	−0.179	−0.164	−0.116	−0.114	−0.114	−0.117	−0.145	−0.097	0.015	0.148	0.116
ACTq1	P	**0.003**	**0.007**	**0.009**	**0.027**	0.127	0.080	**0.031**	**0.007**	**0.044**	0.327	**0.012**	**0.023**
	r	−0.163	−0.154	−0.148	−0.124	−0.087	−0.100	−0.121	−0.154	−0.113	0.055	0.143	0.129
ACTq2	p	**0.004**	**0.003**	**0.008**	**0.004**	**0.031**	**0.020**	0.175	**0.034**	0.389	0.101	**0.002**	**0.003**
	r	−0.160	−0.166	−0.151	−0.161	−0.124	−0.133	−0.077	−0.122	−0.048	0.092	0.175	0.169
ACTq3	p	0.505	0.093	0.195	0.965	0.242	0.561	0.057	0.197	0.100	0.074	**0.032**	**0.011**

(*Continued*)

Table 2 (Continued).

		$R5_{in}$	$R5_{exp}$	$R5_{tot}$	$R19_{in}$	$R19_{exp}$	$R19_{tot}$	$R5\text{-}R19_{in}$	$R5\text{-}R19_{ex}$	$R5\text{-}R19_{tot}$	$X5_{in}$	$X5_{exp}$	$X5_{tot}$
	r	−0.037	−0.096	−0.074	−0.002	−0.067	−0.033	−0.107	−0.074	−0.092	0.100	−0.122	0.144
ACTq4	p	0.076	**0.037**	0.065	0.144	0.488	0.338	0.305	**0.010**	0.549	0.247	0.189	0.806
	r	−0.100	−0.118	−0.105	−0.082	−0.040	−0.055	−0.058	−0.147	−0.034	−0.065	0.075	0.014
ACTq5	p	0.053	**0.038**	0.058	0.129	0.183	0.127	0.145	0.118	0.233	0.878	0.218	0.467
	r	−0.108	−0.118	−0.108	−0.086	−0.076	−0.087	−0.082	−0.089	−0.067	−0.009	0.070	0.042
ACQsum	p	**0.016**	**<0.001**	**0.003**	0.187	0.104	0.124	**0.023**	**0.002**	**0.037**	0.086	**<0.001**	**<0.001**
	r	0.135	0.189	0.167	0.074	0.093	0.088	0.128	0.181	−0.117	−0.097	**−0.213**	−0.192
ACQq1	p	0.170	**0.014**	**0.040**	0.803	0.312	0.515	**0.013**	**0.004**	**0.029**	**0.015**	**<0.001**	**<0.001**
	r	0.077	0.140	0.117	0.014	0.058	0.037	0.140	0.165	0.122	−0.136	**−0.205**	**−0.207**
ACQq2	p	**0.044**	**0.004**	**0.011**	0.301	0.095	0.168	**0.043**	**0.011**	0.075	0.101	**0.017**	**0.009**
	r	0.113	0.166	0.145	0.058	0.096	0.079	0.114	0.145	0.100	−0.092	−0.136	−0.148
ACQq3	p	0.104	**0.032**	0.062	0.448	0.603	0.525	0.195	**0.040**	0.271	0.631	**0.005**	**0.026**
	r	0.091	0.122	0.106	0.043	0.030	0.037	0.073	0.117	0.062	−0.027	−0.161	−0.127
ACQq4	p	**0.029**	**0.008**	**0.020**	0.158	0.194	0.170	0.138	**0.023**	0.214	0.619	**<0.001**	**0.009**
	r	−0.122	0.150	0.132	0.080	0.074	0.079	0.084	0.130	0.070	−0.028	−0.192	−0.148
ACQq5	p	0.076	**0.040**	0.070	0.435	0.456	0.381	**0.032**	**0.002**	**0.031**	**0.015**	**0.003**	**0.002**
	r	0.100	0.117	0.103	0.044	0.043	0.050	0.121	0.172	0.121	−0.136	−0.169	−0.177
MiniAQLQ	p	**0.006**	**<0.001**	**0.003**	0.103	0.121	0.145	**0.019**	**0.003**	**0.035**	**0.010**	**<0.001**	**<0.001**
	r	−0.153	−0.188	−0.170	−0.092	−0.089	−0.084	−0.133	−0.171	−0.119	0.144	**0.224**	**0.219**
HADS	p	0.538	0.197	0.235	0.070	0.082	0.096	0.107	0.640	0.189	0.189	0.505	0.175
	r	0.035	0.074	0.068	0.102	0.099	0.095	−0.091	−0.027	−0.074	−0.074	−0.038	−0.077
Nijmegen	p	**0.003**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.384	0.145	0.458	**0.009**	**0.007**	**0.003**
	r	0.166	**0.207**	**0.201**	0.185	**0.216**	**0.208**	0.049	0.084	0.042	−0.147	−0.153	−0.168
SNOT-22	p	0.160	0.108	0.118	0.364	0.247	0.290	0.410	0.144	0.418	**0.036**	0.180	0.170
	r	0.079	0.092	0.090	0.051	0.067	0.061	0.047	0.084	0.046	−0.118	−0.077	−0.079
MiniRQLQ	p	**0.018**	**0.007**	**0.017**	**0.028**	0.055	**0.048**	0.175	**0.020**	0.290	0.284	0.128	0.070
	r	0.132	0.153	0.135	0.124	0.110	0.113	0.076	0.133	0.059	−0.060	−0.087	−0.103

Notes: Data is shown as p-value (p) and Spearman correlation coefficient (r). Significant p-values are presented in bold.

Abbreviations: ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; q1, question 1; q2, question 2; q3, question 3; q4, question 4; q5, question 5; sum, total; MiniAQLQ, mini version of Asthma Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; Nijmegen, questionnaire that is used to screen patients with dysfunctional breathing such as hyperventilation syndrome; SNOT-22, Sino-nasal outcome test; MiniRQLR, mini version of Rhinoconjunctivitis Quality of Life Questionnaire; R5, Resistance at 5Hz; R19, Resistance at 19Hz; X5, Reactance at 5 hz; in, inspiratory; exp, expiratory; tot, total.

correlations with R5-R19 were observed when the subjects with controlled or uncontrolled asthma were investigated separately.

X5 correlated with total ACT and ACQ, as well as ACTq1-3 and ACQq1-5, when investigating the entire group of patients, specifically in expiratory values (Table 2). In uncontrolled asthma, there were specific correlations between X5 and the total ACQ score, ACQq1 (night symptoms), q2 (morning symptoms), and q5 (wheeze), which were not found in

the controlled asthma (Supplemental Table 3a and b). MiniAQLQ and Nijmegen also correlated with X5 (and both inspiratory and expiratory values) and were mostly controlled compared to uncontrolled disease.

After adjustment for age and sex, the association between ACT and airway obstruction (R5, R19, and X5) was still evident and, similar to unadjusted, primarily in the group of controlled asthma but not in the uncontrolled asthma group (Supplemental Table 4).

Nijmegen Score Cut-off in Relation to Airway Resistance

A cut-off value of 23 for the Nijmegen questionnaire (defining two groups with or without dysfunctional breathing) showed a higher R5, mostly in the expiratory part, but also R19, in subjects with more symptoms (Figure 5).

Nijmegen as Separate Questions and Correlations with FOT Measurements

When investigating all subjects with asthma, R5 and R19 correlated with the scores of many of the questions, most evidently with breathing-related questions, such as faster/deeper breathing, shortness of breath, and inability to breathe deeply, but also with other symptoms, such as blurred vision, dizzy spells and feeling confused (Table 3). All these scores correlated better with expiratory than inspiratory values. X5 was correlated with scores from fewer questions, such as those on having dizzy spells and shortness of breath.

In the uncontrolled asthma group, some questions correlated more strongly with R5 and R19 than those in the asthma group. These were blurred vision, feeling confused and bloated feeling in the stomach, and R19 was additionally

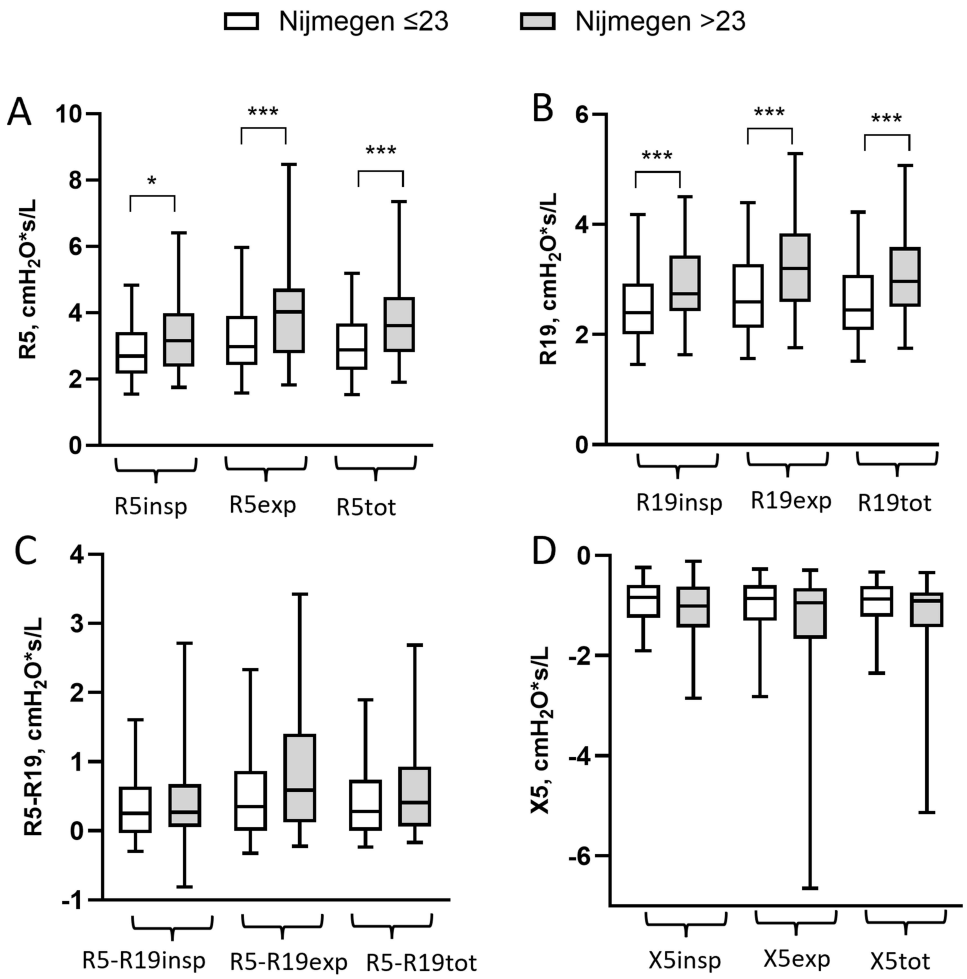

Figure 5 Box-plots of R5 (**A**), R19 (**B**), R5-R19 (**C**) and X5 (**D**) in groups of asthma separated according to Nijmegen ≤ or >23. *=p<0.05, ***=p<0.001 from statistical analyses using Mann–Whitney *U*-test for comparisons between separate groups.
Abbreviations: insp, inspiratory; exp, expiratory; tot, total.

 https://doi.org/10.2147/JAA.S497218

Table 3 Correlations Between the Nijmegen Questionnaire Score (for Separate Questions) and Forced Oscillation Technique Measurements in All Patients (n=319)

		$R5_{in}$	$R5_{exp}$	$R5_{tot}$	$R19_{in}$	$R19_{exp}$	$R19_{tot}$	$R5\text{-}R19_{in}$	$R5\text{-}R19_{ex}$	$R5\text{-}R19_{tot}$	$X5_{in}$	$X5_{exp}$	$X5_{tot}$
Q1-chest pain	p	0.678	0.418	0.355	0.660	0.365	0.514	0.861	0.831	0.657	0.395	0.831	0.589
	r	0.023	0.046	0.053	0.025	0.052	0.038	0.010	0.012	0.025	−0.048	−0.012	−0.031
Q2-feeling tense	P	0.099	**0.006**	**0.004**	**0.026**	**0.002**	**0.006**	0.633	0.329	0.537	**0.009**	0.076	**0.014**
	r	0.093	0.158	0.163	0.126	0.174	0.158	0.027	0.056	0.035	−0.147	−0.101	−0.141
Q3-blurred vision	p	**0.009**	**0.001**	**0.002**	**<0.001**	**0.002**	**0.001**	0.277	**0.022**	0.354	0.184	0.086	0.054
	r	0.146	0.185	0.178	0.186	0.177	0.182	0.061	0.131	0.052	−0.075	−0.098	−0.110
Q4-dizzy spells	p	**0.003**	**<0.001**	**<0.001**	**0.006**	**0.004**	**0.004**	0.182	0.133	0.177	**0.022**	**0.013**	**0.010**
	r	0.164	0.193	0.196	0.154	0.163	0.165	0.075	0.086	0.076	−0.128	−0.141	−0.147
Q5-feeling confused	p	**0.023**	**0.004**	**0.003**	**0.002**	**0.001**	**<0.001**	0.973	0.383	0.904	0.384	0.283	0.429
	r	0.128	0.164	0.167	0.172	0.187	0.191	−0.002	0.050	0.007	−0.049	−0.061	−0.045
Q6-faster/deeper breathing	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.209	0.079	0.392	0.114	0.062	0.053
	r	0.201	0.217	0.206	0.221	0.209	0.222	0.071	0.101	0.048	−0.089	−0.106	−0.111
Q7-short of breath	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.036**	**0.007**	0.092	**0.009**	**<0.001**	**<0.001**
	r	0.233	0.250	0.238	0.193	0.197	0.212	0.119	0.153	0.095	−0.146	−0.230	−0.218
Q8-tight feelings in the chest	p	0.749	0.549	0.614	0.504	0.313	0.401	0.564	0.986	0.584	0.227	0.595	0.522
	r	0.018	0.034	0.029	0.038	0.058	0.048	−0.033	0.001	−0.031	−0.068	−0.030	−0.037
Q9-bloated feeling in the stomach	p	0.114	**0.011**	**0.018**	0.421	0.091	0.148	0.061	**0.021**	0.156	0.101	**0.015**	**0.023**
	r	0.089	0.145	0.135	0.046	0.097	0.083	0.106	0.132	0.080	−0.092	−0.139	−0.130
Q10-tingling fingers	p	0.061	0.038	**0.050**	**0.028**	**0.016**	**0.015**	0.191	0.205	0.244	0.107	0.181	0.117
	r	0.105	0.118	0.112	0.124	0.138	0.139	0.074	0.073	0.066	−0.091	−0.076	−0.090
Q11-unable to breathe deeply	p	**0.001**	**0.001**	**0.001**	**0.007**	**0.010**	**0.006**	0.596	0.313	0.554	0.061	**0.003**	**0.007**
	r	0.181	0.180	0.181	0.153	0.148	0.157	0.030	0.058	0.033	−0.105	−0.167	−0.153
Q12-stiff fingers or arms	p	0.104	**0.021**	**0.045**	0.287	0.331	0.333	**0.005**	**<0.001**	**0.016**	0.075	**0.003**	**0.008**
	r	0.091	0.131	0.114	0.060	0.056	0.056	0.157	0.188	0.135	−0.100	−0.168	−0.152
Q13-tight feelings around the mouth	p	0.940	0.976	0.860	0.771	0.545	0.671	0.666	0.884	0.871	0.993	0.798	0.989
	r	−0.004	0.002	0.010	0.016	0.035	0.024	−0.024	−0.008	−0.009	0.001	0.015	0.001
Q14-cold hands or feet	P	0.455	0.441	0.282	**0.025**	**0.002**	**0.007**	0.059	**0.014**	0.141	0.121	0.425	0.742
	r	0.042	0.044	0.062	0.126	0.178	0.153	−0.107	−0.140	−0.083	−0.087	0.046	−0.019
Q15-palpitations	p	0.133	0.339	0.299	0.322	0.358	0.288	0.085	0.444	0.176	0.055	0.628	0.354
	r	0.084	0.055	0.059	0.056	0.053	0.061	0.097	0.044	0.076	−0.108	−0.028	−0.053
Q16-feeling of anxiety	p	0.286	**0.012**	**0.021**	**0.035**	**0.003**	**0.009**	0.223	0.927	0.331	0.153	0.104	0.076
	r	0.060	0.143	0.131	0.119	0.172	0.149	−0.069	0.005	−0.055	−0.080	−0.093	−0.101

Notes: Data is shown as p-value (p) and Spearman correlation coefficient (r). Significant p-values are presented in bold. The Nijmegen questionnaire is used to screen patients with dysfunctional breathing such as hyperventilation syndrome. There are 16 items, Q1-Q16, (related to symptoms of hyperventilation syndrome) to be answered on a 5-point scale ranging from "never" (0) to "very often" (4).

Abbreviations: R5, Resistance at 5Hz; R19, Resistance at 19Hz; X5, Reactance at 5 hz; in, inspiratory; exp, expiratory.

https://doi.org/10.2147/JAA.S497218

correlated with feeling tense, dizzy spells, and shortness of breath (Supplemental Table 5a). Only the question regarding the bloated feeling in the stomach was correlated with X5 in this group.

In the group of patients with controlled asthma (Supplemental Table 5b), R5 and R19 specifically correlated with faster/deeper breathing and shortness of breath, whereas X5 correlated most with the question referring to shortness of breath.

Rhinitis Symptoms and Correlation with FOT Measurements

There were no correlations between the SNOT-22 scores and FOT measurements in the entire group (Table 2). In controlled disease, there were weak correlations between the SNOT-22 score and expiratory R5, R19, and consequently, R5-R19 (Supplemental Table 3b).

Discussion

To evaluate both symptoms and the burden of the disease on patients' QoL, standardised questionnaires must be used. However, it is commonly accepted that questionnaires used worldwide in clinical practice do not adequately measure the entire range of heterogeneous diseases such as asthma. Most questionnaires evaluating symptoms and quality of life were developed several years ago and have not evolved in parallel with the definition of asthma control. Many questions still contribute to the total score of the questionnaires which appear increasingly irrelevant as asthma research progresses, and our understanding of the disease deepens.

The fact that spirometry results and questionnaires correlated well with each other does not necessarily indicate an adequate evaluation method. Presumably, the most widely used asthma-specific questionnaire was originally designed to align with spirometry results. However, in patients with uncontrolled disease, the correlations between asthma symptom score and spirometry results were no longer evident, proposing that spirometry results do not reflect the symptom burden in these patients.

It is interesting that the patients found to have controlled disease based on ACT were not the same when the disease was defined as controlled based on ACQ. The two questionnaires are not comparable because they examine 4- and 1-week periods of symptom duration, respectively, and it is widely accepted that uncontrolled disease varies greatly from week to week. From a patient perspective, the structural differences in the available answers to choose between the ACQ and ACT may be of significant importance, even when it concerns the same questions.

However, there was a statistically significant difference in clinical characteristics between the two groups based on ACT $< $ or ≥ 20, indicating that the two groups were not similar, which is probably why they answered differently to the other questionnaires besides ACT.

There was a significant correlation between FOT measurements and the most commonly used questionnaires, ACT, ACQ, and MiniAQLQ, which evaluate the symptoms and quality of life in patients with asthma. In addition, measurements of resistance and reactance during expiration correlated better with questionnaires, as expected. Furthermore, as mentioned above, questions related to nighttime symptoms (ACTq3 and ACQq1) provide different results when considering a 4-week period over a 1-week period, reflecting the fluctuations between the obstructive and non-symptomatic states of the lungs in asthma.

To investigate asthma symptoms beyond the classical asthma questionnaires, the less-used questionnaire, Nijmegen, was used in an attempt to include also other symptoms that could relate to the asthma disease. Interestingly, Nijmegen score appeared to correlate consistently with all FOT parameters when evaluating the asthma group as a whole. Theoretically, based on clinical experience, we noticed that the questions included in this tool are perhaps more relevant when it comes to asthma, which affects peripheral airways. Surprisingly, Nijmegen contains many questions that correlate with R5 and R19, even in uncontrolled disease, which was not observed in controlled disease. This suggests that the Nijmegen is a better tool for capturing a broad range of symptoms that are otherwise difficult to identify in uncontrolled asthma. However, this was not the case for X5, which appears to express airway dysfunction in controlled asthma. In previous studies, X5 was identified as a potential marker for differentiating healthy, asthmatic, COPD, and ILD subjects from one another.[30]

The lack of correlation between HADS and FOT measurements showed that airway obstruction was not related to depression status. In addition, this indicates that the symptoms are not explained by psychological factors; instead, true peripheral obstruction is more likely to be present.

Although the difference between R5 and R19 (R5-R19) is believed to be a good indirect marker of peripheral obstruction, no significant correlation was observed between ACT and total R5-R19 in the present study. One could argue that the questionnaires lacked the ability to capture any grade of obstruction in the peripheral airways; however, the explanation appears to be more complicated. We noticed that R5 (both inspiratory and expiratory) correlated with the total symptom questionnaire scores from ACT and ACQ, regardless of asthma control. However, R19 correlated with ACT only in the group with controlled disease. One could argue that there is no significant change in R19, reflecting obstruction at the central level when symptoms, evaluated by the ACT, develop. However, we noticed a correlation between Nijmegen and R19 when investigating the asthma group as a whole regardless of disease control. The relationship between the symptoms and peripheral obstruction has previously been questioned and requires further investigation.[31]

Based on the above-mentioned observations, we applied different cut-off points to detect significant differences in the peripheral airways among the patient groups. The results, when choosing several ACT cut-off points, exhibited a different aspect compared to the usual ACT cut-off at 20 or even the ACQ-5 cut-off points at 0.75 and 1.5. Symptom severity, as examined using the ACT questionnaire, reflects changes in peripheral resistance and reactance. However, this was not achieved when a cut-off point of 20 was used. Presumably, patients with total scores below 20, but also those with a total score between 20 and 25, are heterogeneous groups that need to be examined separately when trying to understand whether the disease is under control and to what degree.

Although the uncontrolled asthma group was smaller than the controlled group, which is a limiting factor that may have undependably affected the results, previous studies indicated that neither the ACT nor the ACQ is reliable for the assessment of uncontrolled asthma.[7] Many of the correlations were weak, reflecting the heterogeneity of the asthma populations as well as the subjective nature of using self-filled in questionnaires.

The real-life study design included patients with asthma without a strict definition of asthma itself or a concrete asthma diagnosis other than that based on the knowledge of the study participants. However, the diagnosis of asthma was re-evaluated by a physician when all lung function tests were completed. GINA staging was not evaluated because information regarding both medication dosage and compliance was lacking.

A strength of this study is that the participants completed a large number of questionnaires on the same day and at the same time they also performed FOT measurements. Thus, among these multiple comparisons, there is a risk of false positive correlations, but since obvious patterns could be found, these are more reliable than isolated findings. In addition, all FOT measurements were supervised by experienced personnel at two sites specialised in asthma.

In conclusion, the grade of symptoms and quality of life in patients with asthma assessed using questionnaires such as the ACT, ACQ, and AQLQ correlated well with peripheral airway obstruction. A correlation was observed even for non-specific asthma questionnaires such as Nijmegen, which revealed airway obstruction, specifically in uncontrolled asthma. Resistance and reactance measured during expiration were the most pronounced, suggesting an association between expiratory flow limitation and an increased symptom burden.

Acknowledgments

We would like to thank the staff at Näsets läkargrupp and at the Lung and Allergy Unit, Skåne University Hospital for their valuable help and support.

Funding

This study was financially supported by independent research grants from Interreg ÖKS [NYPS20201002], The Swedish Heart and Lung Foundation, The Swedish Asthma and Allergy Association´s Research Fund, AstraZeneca, and TEVA. The funders were not involved at any stage of the project.

Disclosure

The authors report no conflicts of interest in this work.

References

1. GINA. GINA main report 2023. Available from: https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. Accessed March 20, 2025.
2. Heijkenskjold Rentzhog C, Janson C, Berglund L, et al. Overall and peripheral lung function assessment by spirometry and forced oscillation technique in relation to asthma diagnosis and control. *Clin Experimental Allergy*. 2017;47(12):1546–1554. doi:10.1111/cea.13035
3. Wilson SR, Rand CS, Cabana MD, et al. Asthma outcomes: quality of life. *J Allergy Clin Immunol*. 2012;129(3 Suppl):S88–123. doi:10.1016/j.jaci.2011.12.988
4. Apfelbacher CJ, Hankins M, Stenner P, Frew AJ, Smith HE. Measuring asthma-specific quality of life: structured review. *Allergy*. 2011;66(4):439–457. doi:10.1111/j.1398-9995.2010.02500.x
5. Lurie A, Marsala C, Hartley S, Bouchon-Meunier B, Dusser D. Patients' perception of asthma severity. *Respir Med*. 2007;101(10):2145–2152. doi:10.1016/j.rmed.2007.05.027
6. Wildhaber J, Carroll WD, Brand PL. Global impact of asthma on children and adolescents' daily lives: the room to breathe survey. *Pediatric Pulmonol*. 2012;47(4):346–357. doi:10.1002/ppul.21557
7. Jia CE, Zhang HP, Lv Y, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol*. 2013;131(3):695–703. doi:10.1016/j.jaci.2012.08.023
8. Aronsson D, Tufvesson E, Ankerst J, Bjermer L. Allergic rhinitis with hyper-responsiveness differ from asthma in degree of peripheral obstruction during metacholine challenge test. *Clin Physiol Funct Imaging*. 2008;28(2):81–85. doi:10.1111/j.1475-097X.2007.00772.x
9. Anderson WJ, Zajda E, Lipworth BJ. Are we overlooking persistent small airways dysfunction in community-managed asthma? Annals of allergy, asthma & immunology: official publication of the American College of Allergy. *Asthma Immunol*. 2012;109(3):185–9e2.
10. Postma DS, Brightling C, Baldi S, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. *Lancet Respir Med*. 2019;7(5):402–416. doi:10.1016/S2213-2600(19)30049-9
11. Stenberg H, Diamant Z, Ankerst J, Bjermer L, Tufvesson E. Small airway involvement in the late allergic response in asthma. *Clin Experimental Allergy*. 2017;47(12):1555–1565. doi:10.1111/cea.13036
12. Siddiqui S. Moving closer to clinical application of the forced oscillation technique in asthma monitoring? *Respirology*. 2021;26(6):522–523. doi:10.1111/resp.14083
13. Paredi P, Goldman M, Alamen A, et al. Comparison of inspiratory and expiratory resistance and reactance in patients with asthma and chronic obstructive pulmonary disease. *Thorax*. 2010;65(3):263–267. doi:10.1136/thx.2009.120790
14. Cottini M, Licini A, Lombardi C, Berti A. Prevalence and features of IOS-defined small airway disease across asthma severities. *Respir Med*. 2021;176:106243. doi:10.1016/j.rmed.2020.106243
15. Nasr A, Papapostolou G, Jarenback L, et al. Expiratory and inspiratory resistance and reactance from respiratory oscillometry defining expiratory flow limitation in obstructive lung diseases. *Clin Physiol Funct Imaging*. 2024;44(6):426–435. doi:10.1111/cpf.12895
16. Aarli BB, Calverley PM, Jensen RL, et al. The association of tidal EFL with exercise performance, exacerbations, and death in COPD. *Int J Chronic Obstr*. 2017;12:2179–2188. doi:10.2147/COPD.S138720
17. Backer V, Klein DK, Bodtger U, et al. Clinical characteristics of the BREATHE cohort - a real-life study on patients with asthma and COPD. *Eur Clin Respir J*. 2020;7(1):1736934. doi:10.1080/20018525.2020.1736934
18. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65. doi:10.1016/j.jaci.2003.09.008
19. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553–558. doi:10.1016/j.rmed.2004.10.008
20. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta psychiatrica Scandinavica*. 1983;67(6):361–370. doi:10.1111/j.1600-0447.1983.tb09716.x
21. van Dixhoorn J, Duivenvoorden HJ. Efficacy of nijmegen questionnaire in recognition of the hyperventilation syndrome. *J Psychosomatic Res*. 1985;29(2):199–206. doi:10.1016/0022-3999(85)90042-X
22. van Dixhoorn J, Folgering H. The nijmegen questionnaire and dysfunctional breathing. *ERJ Open Res*. 2015;1(1):00001–2015. doi:10.1183/23120541.00001-2015
23. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34(5):447–454. doi:10.1111/j.1749-4486.2009.01995.x
24. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Europ resp J*. 1999;14(1):32–38. doi:10.1034/j.1399-3003.1999.14a08.x
25. Exhaled NO. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med*. 2005;15(171(8)):912–930.
26. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Europ resp J*. 2012;40(6):1324–1343. doi:10.1183/09031936.00080312
27. Shirai T, Kurosawa H. Clinical application of the forced oscillation technique. *Internal Med*. 2016;55(6):559–566. doi:10.2169/internalmedicine.55.5876
28. Dellaca RL, Santus P, Aliverti A, et al. Detection of expiratory flow limitation in COPD using the forced oscillation technique. *Europ resp J*. 2004;23(2):232–240. doi:10.1183/09031936.04.00046804
29. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Europ resp J*. 2003;22(6):1026–1041. doi:10.1183/09031936.03.00089403
30. Sugiyama A, Hattori N, Haruta Y, et al. Characteristics of inspiratory and expiratory reactance in interstitial lung disease. *Respir Med*. 2013;107(6):875–882. doi:10.1016/j.rmed.2013.03.005
31. Gonem S, Natarajan S, Desai D, et al. Clinical significance of small airway obstruction markers in patients with asthma. *Clin Experimental Allergy*. 2014;44(4):499–507. doi:10.1111/cea.12257