

Influence of rhinitis control and inspiratory loop flattening on perceived asthma control



Patient-reported outcome measures in asthma and rhinitis are important tools for acute and longitudinal disease monitoring. The Asthma Control Test (ACT)^{1,2} and the Rhinitis Control Assessment Test (RCAT)³ are 2 brief, valid measures that can be used to monitor the assessment of patient control of these respective conditions. Children and adults with asthma are frequently noted to have comorbid allergic or chronic (nonallergic) rhinitis and vice-versa.⁴ These conditions can influence each other, and there are emerging hypotheses that suggest there is “one airway” from nose to lung.⁵ Therefore, optimal asthma control could be difficult in the setting of uncontrolled rhinitis. In children, asthma is frequently manifested only by cough in the setting of normal forced expiratory volume in 1 second (if obtainable at pulmonary function testing [PFT]).⁶ Such cough might not be uni-factorial and could consist of multiple components, some representing classic asthmatic airflow obstruction and some not representative of this classic intrathoracic airflow obstruction diagnostic of asthma, creating a situation in which the symptom can mimic asthma. Many adults can have a similar situation, especially if cough symptoms occur in the setting of conditions such as upper respiratory tract infection or exercise that can induce pharyngeal irritation, paradoxical vocal fold motion (“vocal cord disorder”), or postnasal drip induced cough.⁷ Thus, “cough” as a symptom of asthma is often multifactorial, not necessarily specific to the condition, and this might not correlate to objective pulmonary function. Use of the inspiratory flow loop to help discern cough originating from extrathoracic causes could confound a diagnosis of airway obstruction.⁸

The ACT is a validated outcome measure to help predict who is at future risk of severe asthma exacerbations. The index is highly reliable and validated against spirometry and specialist intervention. An ACT score lower than 19 corresponds to poor control and a score lower than 15 corresponds to exceptionally poor control (sensitivity 60–70% and specificity 70–75% for these scores), whereas an ACT score higher than 23 indicates good control. The ACT has been criticized as focusing only on severity of symptoms and not on severity plus other objective measures.^{1,2} However, the ACT has good receiver operating characteristics for predicting Global Initiative for Asthma level of asthma control.⁹ Clinically, cough alone might be associated with a low ACT score in the setting of otherwise normal spirometry result with the exception of aberrations of the inspiratory loop, which would clinically correspond to an extrathoracic component of cough that would not represent asthma or poor asthma control and masquerade as poorly controlled asthma.^{7,8} Such an individual might not benefit from additional asthma control interventions, leading to misdiagnosis, unnecessary medication, and potentially unnecessary health care expenditure. We sought to better define a cross-sectional relation between PFT results and ACT score in patients, the influence of the 6-item RCAT (a validated rhinitis patient-reported scoring measure with a score >21 indicating good rhinitis control),³ and better understand whether particular domains of the ACT might be

associated with spirometry flow-volume loop patterns indicating an extrathoracic source of dysfunction.

We retrospectively reviewed 251 pediatric and adult patients seen from March to July 2015 at the University of Michigan Division of Allergy and Clinical Immunology clinics (Ann Arbor). Patients were included if an ACT was performed. Chart review was performed to determine the clinical impression of the encounter, medication usage, presenting symptoms, asthma history, PFT result including flow-volume loop impression, RCAT score, allergic sensitization, and comorbidities. We examined spirometry flow-volume inspiratory loops for evidence of flattening indicative of variable inspiratory obstruction that suggested extrathoracic causes of symptoms could be a contributing factor. Data were recorded in an Excel spreadsheet (Microsoft, Redmond, Washington), uploaded to STATA SE 13 (StataCorp, College Station, Texas), and analyzed for descriptive statistics of the population and inferential trends by Student *t* test and multiple logistic or linear regression. This study was approved by the institutional review board of the University of Michigan.

Population demographics, including baseline asthma status and median scores for the ACT, RCAT, and PFT parameters, are presented in Table 1. The 2 indices showed a high degree of relatedness in this population. High ACT score was associated with a higher predicted RCAT score, adjusted for PFT parameters, age, and inspiratory loop flattening (coefficient 0.56, 95% confidence interval [CI] 0.35–0.76, $P < .001$). Only 2 childhood ACT domains (daytime symptoms, $\rho = 0.4$, $P = .04$; and symptoms with playing, $\rho = 0.45$, $P = .02$) were significantly correlated with the RCAT score. However, multiple adult ACT domains were significantly correlated with RCAT score, including rescue inhaler use ($\rho = 0.41$, $P < .001$), nocturnal symptoms ($\rho = 0.36$, $P < .001$), shortness of breath ($\rho = 0.4$, $P < .001$), and productivity ($\rho = 0.45$, $P < .001$). Multiple RCAT domains (nasal congestion, $\rho = 0.38$, $P < .001$; sneezing, $\rho = 0.22$, $P = .02$; watery eyes, $\rho = 0.4$, $P < .001$; and sleep disturbance, $\rho = 0.39$, $P < .001$) were correlated with higher total adult ACT scores (Table 2). Total RCAT and ACT scores were significantly correlated ($\rho = 0.41$, $P < .001$). Baseline inhaled sensitization was not associated with asthma control or ACT control.

For specific discrimination of populations with inspiratory loop flattening present, age older than 21 years was significantly associated with lower odds of inspiratory loop flattening (odds ratio [OR] 0.1, 95% CI 0.05–0.23, $P < .001$) and with good ACT control (OR 0.41, 95% CI 0.19–0.87, $P = .02$). RCAT or ACT scores indicating good control were not associated with the presence of inspiratory loop flattening. The odds of ACT control were associated with RCAT control (OR 4.7, $P < .001$), adjusted for inspiratory loop flattening. There were no significant differences in individual RCAT or ACT item mean scores when these were stratified by the presence of inspiratory loop flattening. No individual ACT items were predictive of inspiratory loop flattening. However, odds of inspiratory loop flattening were associated with the RCAT items for conjunctivitis (OR 1.5, 95% CI 1.03–2.35, $P = .04$) and sleep interference (OR 1.57, 95% CI 1.01–2.44, $P = .04$; Table 2). Split-half reliability of the ACT or RCAT was not improved with any item removal in patients with inspiratory loop flattening. Neither ACT nor RCAT score was associated with inspiratory loop flattening. Inspiratory loop flattening was associated with a higher odds of a higher forced expiratory flow between 25% and 75% (OR 7.7, 95% CI 1.3–44.9, $P = .02$) but not with any other PFT measure adjusted for age. Inspiratory loop flattening was not associated with provider-rated asthma control in the encounter clinical impression; asthma severity; use of

Disclosures: Dr Greenhawt is an expert panel member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency and Aimmune Therapeutics; is a member of physician or medical advisory boards for Aimmune, Nutricia, Kaleo Pharmaceutical, Nestle, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from ThermoFisher, the Aspen, New York, and Swineford allergy societies, the ACAAI, and the EAACI; and is a member of the Joint Taskforce on Allergy Practice Parameters. However he has no relevant conflicts of interest for this report. Ms Wilson reports no conflicts of interest.

Table 1
Population Baseline Demographics (N = 256)

Characteristic	n (%)
Male	122 (48)
Race	
White	206 (80)
Black	27 (11)
Asian	9 (4)
Unspecified	14 (5)
Insurance	
Private	232 (91)
Medicare	22 (7)
Medicaid	1 (<1)
Age	
Pediatric (range 5–21 y)	105 (41)
Adult (range 22–97 y)	151 (59)

long-acting β -agonists, inhaled steroids, leukotriene therapy, or oral steroid in the prior year; use of nasal steroids; baseline inhalant sensitization; or change in medication at the encounter.

In this brief report, within our clinic population we found limited value in the interpretation of inspiratory loop flattening on the performance of the ACT or RCAT in the cross-sectional evaluation of patients with asthma in our clinic sample. This is an important negative finding that will influence clinical management at our center, de-emphasizing this parameter when interpreting these indices in patients with asthma and comorbid rhinitis. Although theoretically such flattening could represent evidence of variable inspiratory obstruction at the extrathoracic level,⁸ its presence did not affect the mean score or any individual domain of the RCAT or ACT, did not affect the interpretation of control based on either index total score, did not affect any specific PFT parameter, and did not have an association with medication use patterns. We denote neither value nor necessity in rescaling either index in the setting of inspiratory loop flattening to assist in clarifying the nature of the diagnosis. Our review did note that ACT and RCAT performance are relatively predictive of each other, emphasizing some evidence for the importance of the influence of control of one condition on the other, and we will continue to coadminister these patient-reported indices together, because they do show value in assisting our management. Alternatively, control of these

conditions could simply tend to trend together but not in a causal manner. These relations with the inspiratory loop, PFT parameters, ACT and RCAT scores, and clinical impressions will help our clinic adjust its decision-making going forward as to how it views the value of possible variable inspiratory obstruction in the evaluation of patients with asthma.

This study was limited by several factors. These describe local trends within our clinic and do not necessarily represent generalizable knowledge because our focus was our outcome measures administered to all patients with asthma and allergic rhinitis as part of our routine clinical care. Furthermore, it was exploratory in nature, was cross-sectional, did not evaluate the trend-in-time performance and significance of inspiratory loop findings, and occurred only during a single allergen season (spring), all of which could potentially influence the results. Because these data are specific to our large referral center and our practice style, they unequivocally need replication and evaluation in our clinic and in other settings, with larger numbers, in particular of younger children, before this could be considered generalizable knowledge. Although our pediatric numbers were good, given that inspiratory loop flattening was more likely to be present in this age group, additional patients could have influenced the findings. It is the general practice of the clinic to not offer PFT assessment to children younger than 5 years, and that even those 5- and 6-year-olds who can perform PFTs often struggle with reproducibility and ability to exhale for 6 seconds. Thus, this study does exclude or likely underrepresents younger children for these technical reasons. Of note, technicians performing the PFTs are trained to pay attention to reproducibility of the inspiratory loop and do not just focus on the expiratory loop reproducibility. In addition, we did not analyze a ratio of inspiratory to expiratory as an additional measure of variable inspiratory obstruction and instead relied on gross appearance in shape and predicted inspiratory volume according to the calculated algorithm of the spirometer. This is a technique to consider for future study.

In conclusion, although the presence of inspiratory loop flattening might be a telltale sign of a variable inspiratory obstruction that can mimic asthma, in our patient review we found no evidence that it provided utility in discerning patients with asthma based on PFT result, ACT and RCAT scores, medication use, and overall asthma severity and provider rating of control. We recommend replication and follow-up study in our and other settings to better evaluate whether the lack of utility is unique to our clinic or if there is general lack of value in this particular finding as a potential outcome measure in general.

Table 2
Associations Between Rhinitis Control and Asthma Control Indices

	ρ	P value
Childhood ACT domains significantly correlated with RCAT score		
Daytime symptoms	0.4	.04
Symptoms with playing	0.45	.02
RCAT domains significantly correlated with higher ACT score		
Nasal congestion	0.38	<.001
Sneezing	0.22	.02
Watery eyes	0.4	<.001
Sleep disturbance	0.39	<.001
Adult ACT domains significantly correlated with RCAT score		
Rescue inhaler use	0.41	<.001
Nocturnal symptoms	0.36	<.001
Shortness of breath	0.4	<.001
Productivity	0.45	<.001
	OR (95% CI)	P value
RCAT item association with odds of inspiratory loop flattening		
Conjunctivitis	1.5 (1.03–2.35)	.04
Sleep interference	1.57 (1.01–2.44)	.04

Abbreviations: ACT, Asthma Control Test; CI, confidence interval; OR, odds ratio; RCAT, Rhinitis Control Assessment Test.

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Assessing hypoxia risk during air travel after a severe asthma exacerbation in children



Decreased atmospheric cabin pressure in commercial aircrafts (cruising altitude 9,000–13,000 m), requiring cabin pressurization from 1,530 to 2,440 m, is equivalent to breathing a fraction of inspired oxygen (FiO_2) of 15.1% at sea level.

These conditions can cause severe hypoxia in patients with chronic respiratory disease. The normobaric hypoxic challenge test (HCT) is the recommended method to estimate the risk of in-flight hypoxia in patients with respiratory disease, allowing symptom observation and titration of oxygen (O_2) requirements.¹ Asthma is reported to be the most common potentially life-threatening condition encountered during flight.² Different guidelines assessing fitness to fly have been published, but there are no specific recommendations for hypoxia risk or for how long the flight should be postponed after hospitalization for asthma exacerbation with O_2 requirements.^{1,3,4}

Our main objective was to determine hypoxia risk during air travel after hospitalization for severe asthmatic exacerbation by performing the HCT in children. A secondary objective was to determine the risk of hypoxia during the HCT in relation to lung function and other conditions.

This prospective study was performed at a pediatric pulmonary function testing laboratory in a tertiary care hospital. Ethics approval was granted (IBNo1867/12 PI). All parents signed informed consent.

We included patients (2–15 years old) hospitalized for severe asthma exacerbation with O_2 dependence (baseline O_2 saturation [SpO_2] < 92%) who were planning a flight after discharge. Exclusion criteria were respiratory (except asthma), cardiovascular, neurologic, or hematologic diseases. Epidemiologic data, clinical variables, duration of hospitalization, and use of O_2 therapy were collected. After completing 24 hours without a need for O_2 , including feeding and sleeping periods (baseline $\text{SpO}_2 \geq 92\%$), spirometry was carried out according to American Thoracic Society and European Respiratory Society guidelines. Then, the HCT was performed according to the recommended method¹ by introducing nitrogen (50 L/min) in a sealed body plethysmograph (Jaeger MasterScreen Body, Becton-Dickinson, Franklin Lakes, New Jersey) that lowered FiO_2 from 21% to 15%, simulating hypoxia during air travel. SpO_2 and heart rate were monitored by continuous pulse oximetry. If SpO_2 decreased to lower than 90%, we titrated O_2 until hypoxia was resolved ($\text{SpO}_2 > 92\%$). Patients who remained with an SpO_2 higher than 90% at an FiO_2 of 15% for 20 minutes were considered a “no in-flight hypoxia risk.” Those who did not were requested to repeat the HCT after 24 hours.

For statistical analysis we used SPSS 12.0 (SPSS, Inc, Chicago, Illinois). To test the hypothesis and analyze the correlation between lung function parameters and HCT outcomes, we performed the Mann-Whitney test.

Fifty-one children (27 boys, mean age 6.5 years, range 2.5–12.2) were recruited from January 2014 through December 2016. Demographic and clinical data such as spirometry and HCT results are listed in Table 1. Forty-six of 51 children (90%) passed the HCT after 24 hours without O_2 therapy and were considered a no in-flight hypoxia risk. Of those 5 of 51 (10%) who did not pass, the HCT was repeated after 48 hours without O_2 and all (100%) passed the test. Mean decrease in SpO_2 while performing the HCT was 4.5%. Patients who did not pass the HCT within the first 24 hours showed lower mean forced expiratory volume in 1 second (FEV_1) compared with the group who passed the HCT (FEV_1 69% vs 89%, $P = .038$). No differences were found in SpO_2 before the HCT, days of hospitalization, required O_2 , and maximum FiO_2 . No significant side effects while performing the HCT were observed.

Because of socioeconomic changes, the number of air travel passengers has been increasing steadily in recent years. During air travel PaO_2 can decrease to 60 mm Hg in travelers without pulmonary disease, causing mild hypoxia, but the shape of the oxygen-hemoglobin dissociation curve usually prevents SpO_2 decreases lower than 92%. In patients with respiratory diseases, SpO_2 decreases are more severe. Sometimes air travel after hospitalization for asthmatic exacerbation is unavoidable. Unfortunately, there is a lack of recommendations for how long air travel should be delayed after hospital discharge.

Most guidelines consider pulse oximetry or arterial gasometry values when selecting patients with hypoxia risk during flights. In fact, patients with PaO_2 higher than 70 mm Hg or SpO_2 higher than 95% are considered fit to fly in most cases. Nevertheless, in recent years, different studies have shown that the “fit-to-fly criteria” based on basal PaO_2 are insufficient.^{3,5} Equations might be used to predict in-flight PaO_2 ; however, these equations are derived from patients with chronic obstructive pulmonary disease, interstitial lung disease, and cystic fibrosis. Their precision remains unclear in patients with asthma but improves in those with other lung diseases after introducing FEV_1 or ratio of FEV_1 to forced vital capacity values.^{6,7} Particularly in adult patients with severe asthma, baseline O_2 saturation appears to be a poor predictor for the need for in-flight O_2 .⁸

Performance of the HCT offers several advantages over equations. It is an individual and more accurate evaluation and allows for an observation of clinical signs of hypoxia. Nevertheless, the HCT has a number of limitations because cabin pressure and density are not reproduced.

This is the first study assessing in-flight hypoxia risk in children with asthma who were hospitalized for asthmatic exacerbation and required O_2 . Although the reliability of the HCT is under discussion, it still is considered the most appropriate test for preflight evaluation.^{1,9} Despite including patients with high O_2 requirements during hospitalization (FiO_2 up to 100% and 14 days of admission), no increased risk of hypoxia while