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To cite this article: Clyde J. Smith, Michael C. Spaeder, Ronald L. Sorkness & W. Gerald Teague (2019): Disparate diagnostic accuracy of lung function tests as predictors of poor asthma control in children, Journal of Asthma, DOI: [10.1080/02770903.2019.1566471](https://doi.org/10.1080/02770903.2019.1566471)

To link to this article: <https://doi.org/10.1080/02770903.2019.1566471>



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Published online: 21 Jan 2019.



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Disparate diagnostic accuracy of lung function tests as predictors of poor asthma control in children

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ABSTRACT

Rationale: In practice, asthma control is assessed according to symptom burden and office spirometry. However, spirometry poorly tests peripheral lung function, which may be abnormal in asthma. Impulse oscillometry (IOS) and multiple-breath washout (MBW) are novel methods which measure reactance (X5) and ventilation heterogeneity (VH) in the peripheral lung, but how well these tests reflect asthma control is poorly understood. **Objective:** To compare the diagnostic accuracy of tests of large airways caliber (FEV₁, FEV₁/FVC, R20), peripheral zone properties (X5, VH), and airways inflammation (FeNO) as predictors of poor control in asthmatic children (44 poorly controlled/10 controlled). **Methods:** 54 children enriched in severe asthma completed a symptom-based control scale (ACT/cACT) and lung function tests after overnight bronchodilator withhold. The accuracy of each variable to predict poor control was ranked by area under the receiver operating characteristic (ROC) curve, sensitivity and specificity. **Results:** Among measures of large airways caliber, the FEV₁% had the highest ROC curve area, with low sensitivity but perfect specificity. Among measures of peripheral lung function, X5 and VH in the conducting zone had fair curve areas with higher sensitivity but lower specificity compared to the FEV₁%. VH in the acinar zone and FeNO both had poor accuracy. **Conclusion:** Tests of large airway and peripheral zone lung function performed disparately as predictors of poor control in a sample of children enriched in severe asthma. Further studies in a larger sample with more diverse phenotypic features are necessary to validate this preliminary conclusion.

ARTICLE HISTORY

Received 25 September 2018

Revised 26 December 2018

Accepted 4 January 2019

KEYWORDS

Asthma; lung function; impulse oscillometry; asthma control; ACT; lung clearance index; expired nitric oxide

Introduction

Providers of care for children with asthma typically depend on parental endorsements of the child's respiratory symptoms and the results of office-based spirometry to assess control and revise treatment. Although the FEV₁ is widely used to measure airflow limitation in asthma, it is not considered a sensitive test of small airways instability, which is often abnormal in asthma [1]. Instead tests of premature airway closure and air-trapping are better predictors of asthma severity and exacerbations than the FEV₁ alone [2,3]. In fact, the FEV₁ is often in the normal range in children and adults with clinically stable but severe asthma [4,5], in whom air-trapping can be present even when the FEV₁/FVC ratio is normal [6]. Therefore, office spirometry may not be a very sensitive method to classify asthma severity and control

and alternate methods to inform treatment decisions might be considered.

It is now widely recognized that asthma can disturb various functional properties of the peripheral or acinar lung zone [1], the so-called “silent region.” The magnitude of peripheral zone dysfunction has clinical relevance with regards to increased rescue medication use [7]. Novel devices to measure the functional properties of the peripheral lung are available but not widely used even in specialty clinical practices. This is largely due to technical complexity, cost and lack of understanding as to what the tests mean and how they relate to patient care. Impulse oscillometry (IOS) measures large and peripheral zone properties, including frequency-dependent small airways resistance (R5–R20) and the reactance at 5 Hz (X5), a test primarily of airways capacitive pressure loss when

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measured at low frequencies [8]. In a community-based study of urban children with relatively mild asthma, small airways measures by IOS performed better than the FEV₁ as predictors of asthma control status [9]. However, 95% of the children with poor control based on general physician assessment in that study had a normal FEV₁%. In a multi-center study in children with poorly controlled asthma undergoing treatment escalation, higher baseline reactance area (AX) was the best predictor of a higher FEV₁ with the addition of a long-acting beta agonist [10]. In a recent prospective study of preschool children, airway resistance measured by IOS was superior to FEV₁ as a predictor of beta agonist use during cough episodes [11].

Multiple-breath washout (MBW) measures the lung clearance index (LCI), the time-dependent clearance of a tracer gas with tidal breathing. LCI data may be partitioned to assess ventilation heterogeneity (VH) in the conducting (Scon) and acinar (Sacin) zones [12]. In children with well controlled asthma and normal FEV₁, the post-bronchodilator LCI was greater than it was in healthy controls, suggesting the method has advantages over spirometry to detect “silent” airway remodeling [13]. Most of the published studies in children have clinically stable and relatively mild asthma, hence MBW deserves further study as a method to assess children with severe asthma and poor symptom control. Furthermore, given the fundamental importance of airway inflammation as a pathological mechanism in asthma, measurement of the breath nitric oxide concentration (FeNO) is widely touted as a useful tool in the assessment of control. However, in one previous study concordance of FeNO with a standard symptom scale metric in children was poor [14].

Relatively few studies have compared the diagnostic accuracy of various lung function methods as predictors of poor control in children with severe asthma. The primary question we wanted to answer was whether a broad panel of tests to examine peripheral lung function perform better than standard measures of large airway caliber by spirometry as predictors of poor control in children with asthma. We designed this study purposely to include a sample enriched in children with frequent symptoms and severe asthma using a composite standard of asthma control based on the widely used symptom scale, the Asthma Control Test (ACT) plus significant exacerbations in the past year. For children under 11 years old, the childhood Asthma Control Test (cACT) was used.

Methods

Fifty-four children with problematic asthma referred to a tertiary academic specialty clinic serving a mixed rural/suburban population participated in the study. Inclusion criteria were (1) physician diagnosis with conformation of bronchodilator reversibility (change in FEV₁% of $\geq 12\%$ from pre-bronchodilator baseline), (2) daily treatment with asthma controller medications [15], (3) no major exacerbations requiring oral corticosteroid treatment or any change in daily controller therapy for 8 weeks pre-enrollment and (4) the child’s ability to follow instructions and meet the quality assurance standards of the NIH/NHLBI’s Severe Asthma Research Program (SARP) to perform accurate and reproducible spirometry [4]. Children with recent episodes of poor asthma control treated by short-acting beta agonists alone were included. Severe asthma was defined according to the ERS/ATS consensus publication in children who required high-dose daily inhaled corticosteroids or maintenance prednisone to maintain asthma control [16]. Exclusion criteria were a diagnosis of major chronic disorders, except asthma, including congenital heart disease, or chronic lung diseases including bronchiectasis, cystic fibrosis, interstitial lung disease, major systemic disorder, bronchopulmonary dysplasia and premature birth (<36 weeks). The study was approved by the local Institutional Review Board; parents provided written consent and the children assented verbally.

Participants withheld ICS/LABA combination medications overnight and short-acting bronchodilators within 6 hours of the study visit. Visit procedures included vital signs, details of past exacerbations and completion of a validated symptom control scale, the cACT/ACT [17]. Children then underwent a sequence of lung function tests (in order); MBW (Exhalyzer D System, Eco Medics AG, Duernten, Switzerland), IOS (BD Care Fusion, Vmax Encore system, Yorba Linda, CA), expired nitric oxide (NIOX Vero, Circassia, Oxford UK) and spirometry (KoKo Sx, Nspire Health, Longmont CO). Two research coordinators trained and certified by the NIH/NHLBI Severe Asthma Research Program (SARP) [4] administered the lung function tests. Procedures for MBW and IOS were followed according to published guidelines [18,19]. Spirometric data were adjusted for sex, height, age, weight, and race and expressed as percent predicted according to NHANES III and Wang et al. reference standards [20,21]. MBW and IOS data were expressed as the raw data with cut points for abnormal values as more than or less than 1.64 *z* scores (5th–95th

Table 1. Subject features.

	Controlled ^a	Poorly controlled	Total	<i>p</i> value
<i>n</i> (%)	10 (18.5)	44 (81.5)	54	
Age (years) ^b	11.7 (7.2–14.7)	10.7 (8.6–13.5)	10.7 (8.3–13.5)	ns
Male <i>n</i> (%)	6 (60.0)	27 (61.4)	33 (61.1)	ns
BMI (% predicted)	54.5 (31.2–82.2)	79.0 (55.0–95.7)	77.0 (53.0–95.0)	ns
Obese <i>n</i> (%) ^c	2 (20.0)	20 (45.5)	22 (40.7)	ns
Race <i>n</i> (%)				ns
White	8 (80.0)	22 (50.0)	30 (55.6)	
Black	1 (10.0)	19 (43.2)	20 (37.0)	
Mixed	1 (10.0)	3 (6.8)	4 (7.4)	
Birth gestational age (months)	40.0 (37.5–40.0)	39.0 (37.3–40.0)	39.5 (37.7–40.0)	ns
Severe asthma <i>n</i> (%) ^d	4 (40.0)	31 (70.5)	35 (64.8)	.06
Daily ICS dose (mcg fluticasone equivalent)	320 (200–800)	420 (200–800)	400 (200–800)	ns
High dose ICS <i>n</i> (%)	4 (40.0)	26 (59.1)	30 (55.6)	ns
Maintenance prednisone <i>n</i> (%)	2 (20.0)	7 (15.9)	9 (16.7)	ns
ICS/LABA combination <i>n</i> (%)	4 (40.0)	28 (63.6)	32 (59.3)	ns

^aACT ≥ 20 and no hospitalizations in the past year.

^bMedian $\pm$ (25th–75th %ile).

^cBMI $\geq$ 85th percentile for age.

^dPer ERS/ATS consensus definition [15].

percentile) derived from published reference standards in healthy control populations [9,22–24].

Data analysis

Poorly controlled asthma was defined according to a composite index based on a cACT/ACT value of ≤ 19 [25] plus one or more exacerbations requiring prednisone therapy in the previous year. The diagnostic accuracy of scaled test measures was ranked by the area under the receiver operating characteristic (ROC) curves with poor control (1 or 0) as the state variable [26–27].

There was no *a priori* sample size estimate as we had no background data for the novel composite asthma control indicator used in the study. Results for scaled data were expressed as the median and IQR (25th–75th %ile) and between group (controlled versus poorly controlled) comparisons with the Mann–Whitney U test. Between group comparisons for categorical data were made with Fisher's exact test. Univariate correlations between the symptom scale data and specific variables were made with Spearman's rho test. A *p* values < 0.05 was the threshold value for refuting the null hypothesis.

Results

Sample features

The sample included 54 children, mostly males (61%), with a median age of 10.7 years (Table 1). Sixty-five % of the sample met criteria for severe asthma. Non-white minorities were represented (44%). The median body mass index percentile for age was 77% and overweight/obesity was common at 41%. Ninety-four %

were treated with daily ICS, 56% at doses $\geq$ SARP thresholds for high-dose, and 17% with maintenance prednisone. Treatment with combination ICS/LABA pMDI was common (59%).

Ten children (18.5%) met the composite definition for controlled asthma, 44 (81.5%) for poorly controlled asthma. There were no significant differences in the demographic and treatment-related features of children with controlled versus poorly controlled asthma with the exception of the proportion with severe asthma, which was more prevalent in children with poorly controlled (70%) versus controlled (40%) asthma.

Test measures compared according to control status

Lung function test results were compared according to asthma control status (Table 2 and Figure 1). All four measured variables by spirometry were significantly lower in children with poorly controlled versus controlled asthma. By contrast, only lower reactance (X5) and higher resonance frequency and none of the remaining IOS measures were different according to control status. With MBW, although LCI and Sacin were not different according to control status, Scond and Scond % were significantly higher in children with poorly controlled versus controlled asthma. FeNO was not significantly different in children with controlled versus poorly controlled asthma.

Correlations of test measures to the cACT/ACT

Correlations between the lung function test values and ACT/cACT scale values were overall fair to poor and none exceeded an absolute value of 0.5 (On-line Supplement Table 1). The best significant correlation

Table 2. Test results compared according to asthma control status.

Spirometry				
	Controlled <i>n</i> = 10	Poorly controlled <i>n</i> = 43	Total	<i>p</i> value
FEV ₁ % predicted	110 (95–115)	93 (75–99)	95 (83–104)	.001
FVC % predicted	113 (97–121)	102 (91–109)	104 (92–113)	.03
FEV ₁ /FVC % predicted	97 (91–104)	89 (81–98)	91 (82–100)	.02
FEF _{25–75} % predicted	110 (90–120)	69 (50–92)	74 (56–99)	.001
Impulse oscillometry				
	Controlled <i>n</i> = 10	Poorly controlled <i>n</i> = 42	Total	<i>p</i> value
R5 Hz (cm H ₂ O/l/sec)	5.1 (3.8–14.3)	7.4 (5.6–8.7)	7.1 (5.3–8.9)	ns
R20 Hz (cm H ₂ O/l/sec)	3.4 (3.1–6.2)	4.8 (4.0–6.1)	4.7 (3.6–6.1)	ns
R5–R20 Hz (cm H ₂ O/l/sec)	2.0 (0.5–5.7)	2.5 (1.3–3.5)	2.3 (1.2–3.6)	ns
X5 (cm H ₂ O/l/sec)	–1.2 (–2.2–0.4)	–1.9 (–2.9–1.5)	–1.7 (–2.8–1.3)	.01
Resonance frequency (Hz)	11.3 (5.7–17.9)	18.4 (13.1–25.2)	17.4 (10.8–24.8)	.02
Multiple-breath Washout				
	Controlled <i>n</i> = 9	Poorly controlled <i>n</i> = 34	Total	<i>p</i> value
LCI 2.5%	7.1 (6.6–9.3)	7.9 (7.2–9.5)	7.8 (7.1–9.5)	ns
LCI 2.5 % predicted	108 (101–147)	120 (109–146)	119 (109–145)	ns
Scond	.010 (.001–0.017)	.020 (.010–.051)	.019 (.010–.048)	.02
Scond % predicted	79 (57–109)	122 (88–313)	102 (68–288)	.04
Sacin	.077 (.061–0.142)	.079 (.059–0.132)	.077 (.059–0.131)	ns
Sacin % predicted	130 (109–255)	133 (103–230)	132 (107–229)	ns
Expired nitric oxide (FeNO)				
	Controlled <i>n</i> = 9	Poorly controlled <i>n</i> = 41	Total <i>n</i> = 50	<i>p</i> value
FeNO (ppb)	12.0 (8.0–20.2)	16.0 (8.0–32.5)	16.0 (8.0–27.6)	ns

was between the Scond % predicted, which decreased as the ACT/cACT value increased ($r = -0.48$, $p < 0.05$).

Diagnostic accuracy of test measures for poor control

The diagnostic accuracy of individual tests as predictors of poor control in the sample had disparate performance indicators (Table 3). Each of the spirometric test variables had a good to fair performance ranking with statistically significant ROC curve areas, near perfect specificity (0.9–1.0), but relatively low sensitivity (0.07–0.53). Based on a good area under the ROC curve of 0.83, the FEV₁% predicted overall performed best among the spirometric variables with a perfect specificity of 1.0 but was not sensitive (0.28) for poor control. The FEF_{25–75}% had the most even performance indicators among all the test variables, but is widely disregarded in clinical practice in children due to variations in effort and poor test to test reproducibility.

By contrast IOS variables, compared to spirometric variables, overall had greater sensitivity as predictors of poor control, but with lower specificity (Table 3). Total (R5) and large airways (R20) resistance both had relatively low ROC curve areas but with equivalent sensitivity at 0.79. Reactance (X5) and resonance frequency had fair (0.75 and 0.73, respectively) ROC curve areas, with the resonance frequency demonstrating even performance features with fair sensitivity (0.59) and the highest specificity (0.70) among all of the IOS variables.

MBW test variables demonstrated significant scatter in their diagnostic performance. Only the Scond and Scond % had significant ROC curve areas, but the area under the curves was fair. Scond had relatively higher sensitivity but lower specificity than the FEV₁% as a predictor of poor control. Sacin performed poorly with high relatively high sensitivity but low specificity. FeNO had poor diagnostic accuracy with a low and insignificant ROC curve area.

Prevalence of spirometric large airway and peripheral lung abnormalities according to asthma control status

Among children with poorly controlled asthma, 60% had both abnormal spirometry and peripheral lung function (Table 4). However, one-third had normal spirometry with abnormal peripheral zone function ($p = 0.05$). Among the 10 children with controlled asthma, only 20% had normal test values for spirometry and peripheral lung function, whereas 70% had normal spirometry but abnormal peripheral zone function.

Discussion

In daily practice, providers of care often strive to accurately assess asthma control based on symptom recall and the results of office spirometry to inform adjustments in therapy. However, this approach is problematic in so far as objective surveys find that approximately one-half of children with asthma are poorly controlled [28]. Novel methods are now

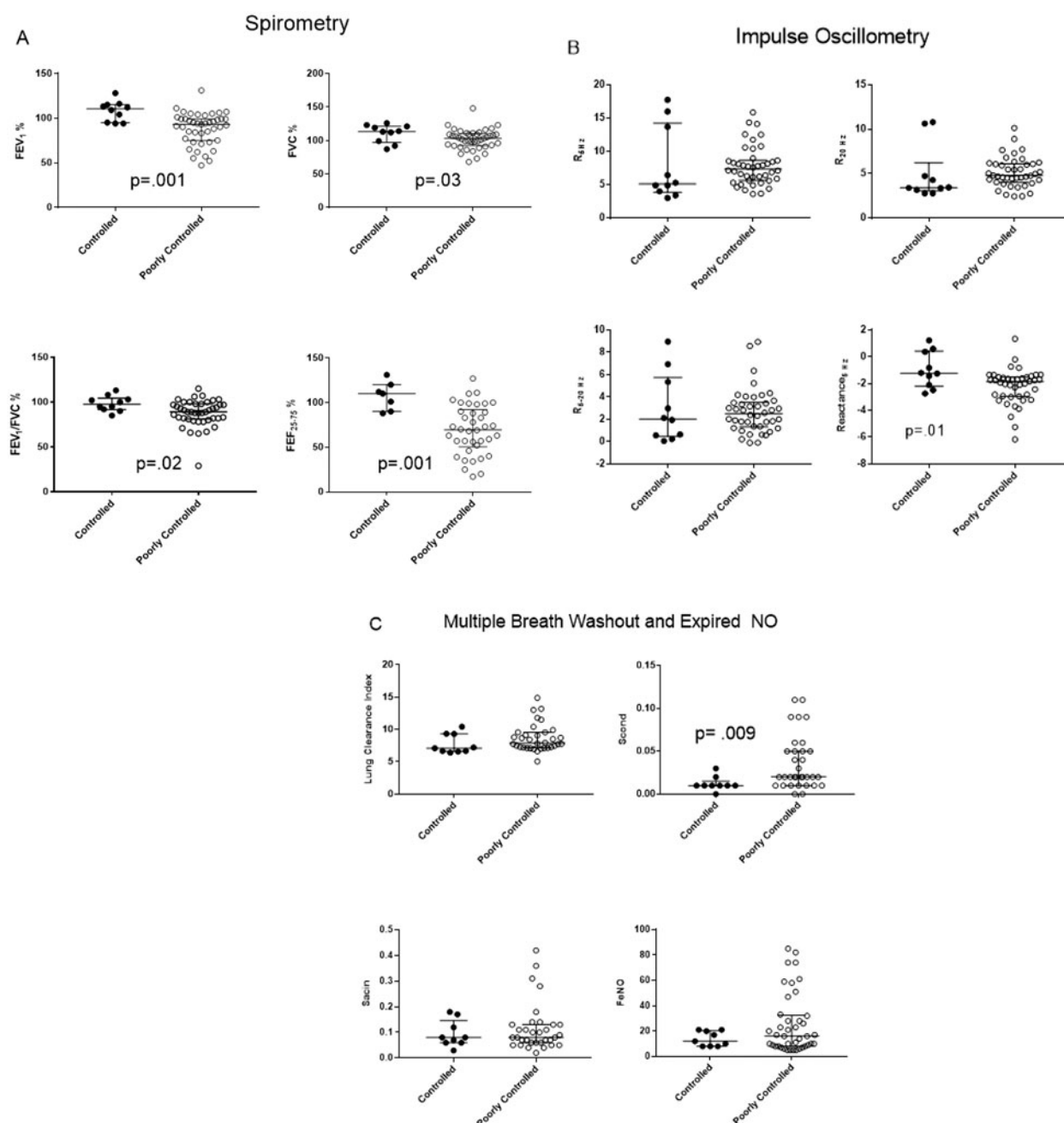


Figure 1. A) Comparison of Spirometry Metrics between controlled and poorly controlled asthmatics. B) Comparison of Impulse Oscillometry metrics between controlled and poorly controlled asthmatics. C) Comparison of Expired NO and Multiple Breath Washout metrics between controlled and poorly controlled asthmatics.

available to measure various physiological perturbations in the peripheral lung not well tested by spirometry. Such measurements might have advantages over spirometric variables as predictors of asthma control, including airways inflammation (FeNO), proximal and peripheral VH (Scond and Sacin), frequency-dependence of resistance (R_5 – R_{20}) and airways capacitance (X_5). Thus, we did the present study to compare the diagnostic accuracy of various methods encompassing a broad spectrum of physiological properties as predictors of poor control in children with asthma.

Whereas the ACT scale is limited by patient recall of symptom burden, we used instead a composite index to define poor asthma control based on significant exacerbations in the past year plus an ACT/cACT value of ≤ 19 .

The most important finding in the study is that the test most widely used in general practice to assess airflow limitation in asthma, the FEV₁%, had a good ROC curve area with perfect specificity as a predictor of poor control. However, in accords with previous studies in children [4,5], the FEV₁% had low

Table 3. Diagnostic accuracy of lung function tests as predictors of poor control in children with severe asthma.

	Poor control +/−	Curve area	Curve rating	95% CI	Sensitivity	Specificity
FEV ₁ % pred.	43/10	.83*	good	.69–.96	.28	1.0
FVC % pred.	42/10	.71*	fair	.51–.90	.07	1.0
FEV ₁ /FVC % pred	43/10	.73*	fair	.58–.88	.53	.90
FEF _{25–75} % pred.	38/7	.88*	good	.78–.99	.50	1.0
R5 ^a	42/10	.62	poor	.36–.97	.79	.60
R20	42/10	.65	poor	.43–.88	.79	.60
R5–R20	42/10	.53	poor	.29–.76	.71	.40
X5 Hz	42/10	.75*	fair	.57–.93	.79	.30
Resonance freq.	42/10	.73*	fair	.58–.87	.59	.70
LCI 2.5 ^b	34/9	.68	poor	.45–.90	.94	.44
LCI 2.5 % pred.	34/9	.68	poor	.45–.90	.76	.56
Scond	33/9	.74*	fair	.58–.89	.42	.89
Scond % pred.	32/8	.73*	fair	.56–.89	.53	.75
Sacin	33/9	.53	poor	.33–.74	.48	.67
Sacin % pred.	33/9	.53	poor	.32–.73	.73	.22
FeNO ppb	41/9	.58	poor	.42–.74	.34	1.0

p*, 0.05.^aSensitivity and specificity based on control status and the number of children with abnormal test values outside of the 25th–75th % ile range in a healthy control sample from references [9, 20–24].^b>1.5 SD above the mean.Table 4.** Lung function patterns in children with asthma.

Poorly controlled <i>n</i> = 44	
Normal spirometry and Normal peripheral zone function 3 (7.0%)	Normal spirometry and abnormal peripheral zone function 14 (33%)
Abnormal spirometry and normal peripheral zone function 0	Abnormal spirometry and abnormal peripheral zone function 26 (60%) ^a
Controlled <i>n</i> = 10	
Normal spirometry and normal peripheral zone function 2 (20%)	Normal spirometry and abnormal peripheral zone function 7 (70%)
Abnormal spirometry and normal peripheral zone function 0	Abnormal spirometry and abnormal peripheral zone function 1 (10%)

^a*p* = 0.05; Fisher's exact test.

sensitivity. Even though our sample was enriched in children with severe asthma, only 12/44 (27%) with poor control had an FEV₁ < 80% predicted. By comparison, tests reflecting the properties of the peripheral lung overall had lower ROC curve areas than spirometric tests sensitive to large airways caliber such as the FEV₁% and FEV₁/FVC%. Peripheral lung measures included the R5–R20, reactance (X5), resonance frequency and VH in the acinar zone, and each had relatively higher sensitivity but lower specificity compared to the FEV₁%. Thus, we found significant disparity in the diagnostic accuracy among the various tests as predictors of asthma control in children. The performance of these tests might also be interpreted based on how providers of care want to use the information. For example, in children with relatively well controlled asthma but a history of frequent lapses in symptom controls, providers might prefer a test that has greater sensitivity for “indolent” peripheral lung dysfunction. Alternatively, for children with a high burden of respiratory symptoms but infrequent exacerbations, providers might want a test that is highly specific so as to avoid over-treatment with oral corticosteroids.

The results of the present study are different from those reported by Shi and colleagues [9] who reported two IOS measures of peripheral lung function, the

frequency dependence of flow resistance, R5–R20 [29], and reactance, as having better diagnostic accuracy than spirometry as predictors of asthma control in children. These disparities likely are due to striking differences in the features of the two study samples. The Shi et al. study addressed children in a community setting with relatively mild asthma; nearly all had normal values of FEV₁%, and were based on physician assessment of asthma control. We found, similar to Shi et al. that X5, a measure of the capacitance of the peripheral lung, was significantly lower in children with poor control versus those with controlled asthma. Furthermore, in our sample X5 had a fair ROC area (0.75) and higher sensitivity than the FEV₁%. To apply the findings of both studies to the care of children with asthma, we would speculate that IOS may be a more useful method in children with mild asthma and a relatively low symptom burden to detect peripheral lung abnormalities. However, in children with severe asthma and a high symptom burden, abnormalities in peripheral lung function are so common that these tests lose specificity as diagnostic adjuncts. Furthermore, there is a paucity of robust clinical trial data to support specific interventions targeted at the peripheral lung in asthma. However, the advent of systemic biological therapies which are not dependent on aerosol delivery devices provides the

opportunity for clinicians to target peripheral lung dysfunction in asthma. Thus, tests of peripheral lung function based on novel methods could have utility.

Overall MBW tests of VH had disparate performance metrics as predictors of poor asthma control in the present study sample. In our hands, despite on site coordinator training, the MBW procedure was not easy to complete in children, with frequent error messages because of inability to meet the rigorous test criteria for acceptability. Furthermore, only Scond, indicative of VH in the branching airways, structures wherein gas flow results from a pressure gradient, had significant diagnostic accuracy for poor control. By contrast, Sacin had poor diagnostic accuracy, primarily due to low specificity. Our results are not dissimilar to those of Macleod et al. [13] who studied children with well-controlled asthma and a normal FEV₁%. They found a substantial degree of VH in the asthmatics compared to healthy controls, and touted the MBW as a potentially useful as test to detect “early” airway disease not apparent from spirometry. Thompson et al. [30] likewise reported significant VH involving the conducting and acinar zones in adults with an exacerbation of asthma and low FEV₁%. Based on regression analysis, the Sacin was the sole contributing factor to the FEV₁%. However, in our sample of clinically stable children both Scon and Sacin correlated poorly with the FEV₁%. Thus, we found Scond to have fair diagnostic accuracy as a predictor of poor control in children with relatively severe asthma and similar to IOS measures its primary drawback was poor specificity.

Methods to assess asthma control have disparate diagnostic performance features. The present study should be interpreted in regards to the limited sample size, particularly with regard to the number of children with controlled asthma and cross-sectional design. Further studies based on a relatively large, characterized sample with diverse features are needed to evaluate which tests of peripheral lung function are most useful to identify children at risk of significant exacerbations. At the present time, we can find no great advantage over standard spirometry of either IOS or MBW in a specialty clinic setting. However, with the advent of biological therapies which can reach the peripheral lung zones, methods sensitive to disease in those areas might have great value and deserve further study.

Acknowledgments

The authors acknowledge the invaluable effort and time committed by the two research coordinators who completed

this study, Kristin Wavell and Theresa Altherr. We also wish to thanks the parents and children who graciously volunteered to participate.

Declaration of interest

The authors have no conflict of interest to declare.

Funding

Grant in aid University of Virginia Children’s Hospital and National Heart, Lung, and Blood Institute (NIH/NHLBI SARP U10 HL109250).

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