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A compendium and review of pediatric pulmonary function testing assessment opportunities for asthma

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Abstract

Objective. Standard spirometers are used in the respiratory disease management community to help diagnosis asthma and provide longitudinal information. Surprisingly, basic information obtained on the spirometer, beyond the FEV₁ and change in FEV₁ after bronchodilator is, however, underutilized. We sought to update the information on pulmonary function and bronchodilator response in children since 2016. We also present here a discussion of other elements of the standard spirometer that can be used for pediatric asthma management.

Data Sources. A Medline search of pulmonary function, children, adolescents, bronchodilator reversibility, small airway disease, small airway function, asthma, airflow limitation, bronchodilator response.

Study Selections. Studies since 2016 that provide information on normal children's (and/or as compared to asthmatic children) bronchodilator response, and addition information on small airway or pulmonary function values after albuterol in asthma.

Results. Limited data has been published on FEV₁ bronchodilator response in children since 2016. Other parameters of the pulmonary function test in children, especially for documenting small airway disease are reviewed here. A priority of PFT results to support the presence of large or small airway disease is presented.

Conclusion. There has been minimal addition published literature on bronchodilator testing for asthma in children since a comprehensive publication in 2016. Other elements of the standard spirometer that can be used for pediatric asthma management beyond the FEV₁ response to bronchodilator, including small airway disease measures is presented. A table of potential pulmonary function test results utilization is presented.

Keywords: Diagnostics, Pediatrics, Physiology

Introduction

Pediatric asthma has followed the adult classification from the simplistic concept of intrinsic to extrinsic to the value-added information of high Type 2, low Type 2, and possibly neutrophilic asthma. (1-6) Adding to the complexity are the concepts of genotyping, phenotyping and endotyping asthma. (7-8) Underlying all classification is the ability to identify a child of having asthma. In fact, asthma is syndromic, and historical syndromes were lumped together due to the lack of qualifying characteristics. Those days have passed.

Well recognized is the absence of a gold standard for asthma diagnosis. A positive methacholine challenge puts the child into a smaller pool of individuals closer to establishing asthma but is NOT a test of absolute certainty. An elevated nitric oxide level similarly supports a clinical impression, but neither an elevated or low nitric oxide level proves or disproves asthma. The presence of bronchoalveolar eosinophils is likely the best test for ascertaining high Type 2 asthma but could miss low Type 2 or neutrophilic variants. The use of inhaled or oral corticosteroid may also reduce or eliminate pulmonary airway eosinophilia at a specific moment in the child's life, and skew bronchial eosinophil recovery from lavage. In addition, bronchoscopy with bronchoalveolar lavage is a rare occurrence in the pediatric asthma diagnosis pathway.

The properly performed pulmonary function test (PFT) comparing pre to post bronchodilator data has become the default method of determining asthma. Results are actually not proof of asthma but rather strong supporting evidence. Compared to methacholine challenge where non-specific airway hyperreactivity is measured by diminished airway function to a bronchoconstricting drug, pre and post bronchodilator PFTs demonstrate improved airway function to a bronchodilator drug, strongly supporting an asthma condition.

The purpose of this paper is to update a review the use of the bronchodilator response of albuterol to the FEV₁ determination in pediatric asthma since a systematic review of the methodology in 2016, (9) and to discuss additional tests that are available to the clinician in the assessment of asthma and asthma severity in children.

The value of a standard pre-post spirometry in all children with potential asthma symptoms far outweighs the costs and time in doing so. Simply put, the baseline PFT (pre-albuterol) is being compared to a mathematically derived set of normative data values. The presence of high predicated results should never dissuade a clinician from obtaining a post-albuterol test. With a pre-post albuterol test the individual is self-comparing, adding value to clinical practice. Additionally, the initial testing can be compared with future testing.

Methods

The Medline literature search strategy used for the previous publication (9) was used for a search strategy for 2016-current, adding terms for small airway disease, small airway function, asthma, airflow limitation. A recent review on small airway disease in pediatric asthma served as a secondary source for pertinent pediatric publications on small airway disease, which adds to the information obtainable for a standard PFT report (10)

Results and Topic Discussion

1. Measurement of FEV₁ after bronchodilator

The pediatric respiratory provider community is well-engrained with a 12% increase in FEV₁ benchmark for a post-albuterol response that is outside of accepted limits. (9) What is not well appreciated is that the 12% change is a 3 (three) standard deviation change (99.7% likelihood) as compared to the baseline FEV₁ for the subject. (9) To state it differently, it would take 333 pre-post albuterol tests to find *one* child who is *NOT* asthmatic and who also has a 12% improvement in FEV₁. That standard is remarkably high. (9)

The use of a 12% change has undergone a prolonged evolution and was extensively reviewed by Hopp and Pasha in 2016. (9) That review provided ample literature evidence that the 12% change in FEV₁, although recognized and accepted, is over-generous. (9)

An update of pediatric pulmonary function epidemiologic or population literature since the 2016 publication is scarce. (9) The yearly update of the Global Initiative on Asthma (GINA) guidelines published in 2020 again stipulates a 12% change in FEV₁ and discusses the utility of the FEV₁/FVC ratio. (11) A review of their bi-annual literature survey (2019) shows only one article in support of the 12% change in FEV₁. (11) However, that study states an 8% change in FEV₁ has a higher sensitivity than a 12% change. (13)

No additional data was found from 2016-2020 to further define a statistically significant versus a clinically significant change in FEV₁ in the diagnosis of asthma in children, but a recently published study in 2021 suggests interest remains (14). Using a segmented logit regression model, the area under the curve and ROC (Receiver Operating Characteristic) of asthma and non-asthmatic children from the **CHildhood ASthma and Environmental Research (CHASER)** study (ClinicalTrials.gov.ID: NCT02433275) was analyzed. (14) The data suggested a 7.9% improvement in FEV₁ and 14.7% improvement were critical values. Under 7.9% an asthma diagnosis almost never occurred, and above 14.9% asthma is almost certain. Their 7.9% is very similar to the conclusion of Hopp and Pasha. (9)

As stated in the article (14), and previously defined (9), asthma as a disease is a moving target and does not have a yes or no test as an *exact* hierarchy for diagnosis. The study did use a logit (yes, no) model, however. (14)

A 2019 study of severe and non-severe pediatric asthma re-affirms the applicability of pulmonary function tests for intra-patient care decisions. (15) The results were limited to FEV₁ and FEV₁ percent predicted, and additional information contained on a standard PFT report was not discussed. (15)

Given the above, are there pulmonary function tests that could be considered to further support an asthma diagnosis and be longitudinally followed for clinical care?

2. Forced vital capacity change after bronchodilator and discussion

The Forced Vital Capacity (FVC) effort in children, especially younger children, may not meet the ATS standards for expiratory time, but experienced technicians and clinicians can use good judgment for deeming baseline repeatability and effort as successful. Techniques on children were reviewed in 2019 by the American Thoracic Society and European Respiratory Society. (16)

A shorter expiratory time with reasonable FVC repeatability can set the baseline to further examine both the total exhaled lung volume and the one second and total expiratory time. After albuterol, and an appropriate wait time, any increase in the FVC on the post-albuterol test can be attributed to a decrease in the functional residual capacity. This coupled with the post-albuterol test for FEV₁ change provides a primary (FEV₁) and secondary (FVC) proof that the albuterol improved volume and flow in both the large airway pool (generation 1-5) and the distal airway pool (beyond generation 5). The data of Sorkness pegs a significant improvement of FVC at 10% after albuterol. (17)

The utilization of FVC was reviewed by Hopp et al in 2020 (10) and that included data on the FVC generated from Sorkness et al (17). The use of FVC has been further validated in adults by the international group headed by Potsma and colleagues. (18) Using the gold standard of chest computerized tomography for determining small airway disease, a low FVC in asthmatic adults was highly associated with the CT findings of small airway disease. (18)

The study of Sorkness extends the baseline FVC data into a z-score perspective; with a baseline z score of -1.64 placing the child's FVC into the lowest 25% of all normal children for normative data, and, as mentioned, a 10% improvement in FVC reflects a significant post-bronchodilator change. (17)

It's very unlikely that albuterol might improve the FVC by 10% without the FEV₁ not also having a significant change (> 12%). To our knowledge, this has not been studied. Interestingly, the change after albuterol (FVC and/or FEV₁) might be accompanied by a shorter expiratory time than the baseline, again directly pointing to the improved flow of previously trapped volume. This information serves as a substitute for a body plesmethography, which looks at air trapping and total lung volume, but at higher costs and less availability. (19)

3. Small airway testing

Unfortunately, the FEF₂₅₋₇₅, an actual measure of medium and small airway function reported on all spirometry tests, has gained an unfavorable reputation. Based, predominately on its wider intra-test differences, it determines a component of airway flow that is real albeit variable enough that it's impact has minimal historical support.

A recently published extensive review of small airway disease in pediatrics emphasizes the important and critical role the small airways plays in asthma. (10) The options to determine small airway disease, outside of the standard spirogram, include body plethysmography, impulse oscillometry, nitrogen washout, or high-resolution CT scans. (18, 19) Each of these have added costs and less availability making them suboptimal test for longitudinal follow-up of airway function.

Lacking practical alternatives, a re-examination of the FEF₂₅₋₇₅ appears reasonable. The clinical utility of the FEF₂₅₋₇₅ test might be supported by tying the test to another accepted pulmonary function value.

An elegant pediatric study by Simon et al provides that association. (20) The demonstration of a low absolute FEF₂₅₋₇₅, less than 65% of predicated at baseline, had a strong correlation with the post-albuterol improvement in FEV₁. This links statistically the known continuous flow between small to large airways in the expiratory phase; and removes the concept of isolating the large from the small airways, and the disfavor of the FEF₂₅₋₇₅ in asthma decision making.

A prominent group of international collaborators are actively assessing and reporting on small airway dysfunction (SAD) in adult asthma. (18) The study is listed at ClinicalTrials.gov and sponsored by Chiesi Farmaceutici S.p.A., with a title of “**Assessment of small Airways involvement In aSthma (ATLANTIS)**, a multinational, multicenter, non-pharmacological intervention, cross-sectional and longitudinal study”. (21) The study goal is to determine a clinically relevant, easy to use methodology of determining SAD in adult asthmatics. (18) The pediatric respiratory provider community is behind in their appreciation and assessment of SAD in children.

There is limited historical discussion of SAD in children. In addition to the recent published extensive review of SAD, there have been other historical pediatric-directed reviews likely beginning with asthmatic adolescents by Hill et al in 1972, (212) followed by assessment of different lung tests in children with asthma and cystic fibrosis compared to controls by Landau et al in 1979. (23)

There are a variety of standard PFT test, and more expensive, and not easily reproducible tests designed to measure small airway dysfunction in children. These include impulse oscillometry, body plesmethography, inert gas wash out, high resolution CT, MRI, gamma scintigraphy, positron emission tomography (PET), single photon emission tomography (SPECT), and alveolar nitric oxide. (18, 19) The applicability of these tests and comment have been recently published. (17) Impulse oscillometry may be a reasonable option, but its availability is limited. (24)

The publication by Potsma and collaborator provides the most recent and most compelling rationale for using standard pulmonary function results in adults to diagnosis SAD, and by reasonable

extension, children. (18) In the study, a volumetric whole lung scan by CT was used to assess the presence of small airway disease. Once the presence of SAD was determined, a battery of pulmonary function tests supporting or “ascertaining” what had been seen on the CT scan were performed. In the adults a decreased forced vital capacity (FVC) followed by the FEF₂₅₋₇₅ and then FEF₅₀ best supported the CT findings of SAD. (18)

A parallel test to FEF₂₅₋₇₅ the MMEF₇₅₋₂₅ has been recently reported in two epidemiological studies of pediatric asthma. (25, 26) Not commonly documented on pulmonary reports, the maximal mid-expiratory flow only provides a less common variation on smaller airway flow.

Tests that are not readily available, or more expensive, such as impulse oscillometry, inert gas washout, or body plesmethography correlated less with SAD than CT scan results. (18) The recent review of SAD in children also summarized these results. (10)

It is reasonable based on the collaborative adult data by Postma (18) that a child with a well performed spirometry could have small airway disease that is reversible (after bronchodilator), based on FEF₂₅₋₇₅ and FEF₅₀, along with a baseline diminished FVC and an improvement in FVC after albuterol. Hierarchies of PFT results that support small airway disease presence have been recently presented and are testable (and being tested) in a clinical study. (18) It seems unlikely that the more tests for small airways are necessary. (18)

Figure 1 provides the location of the proposed tests in a patient with severe large and smaller airway obstruction with marked improvement after albuterol. Table 1 suggests a hierarchy of pulmonary functions test results and their evidence for utilization in clinical practice

Conclusion

Pulmonary function testing continues to be a critical method for pediatric asthma diagnosis and management, and underpins the importance of using PFT in the determination of asthma severity and medication management. Unfortunately, all the information obtainable on a standard PFT is under-utilized for diagnosis and asthma management. We present data, gathered from different sources and collected here, to suggest a strategy for using the standard spirogram for both large and small airway detail and information, which all can be utilized for optimizing pediatric asthma care.

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Test	% Change After albuterol
FVC	93
FEV ₁	93
FEF ₂₅₋₇₅	84
FEF ₅₀	75
MEF ₅₀	68
MMEF ₂₅₋₇₅	84

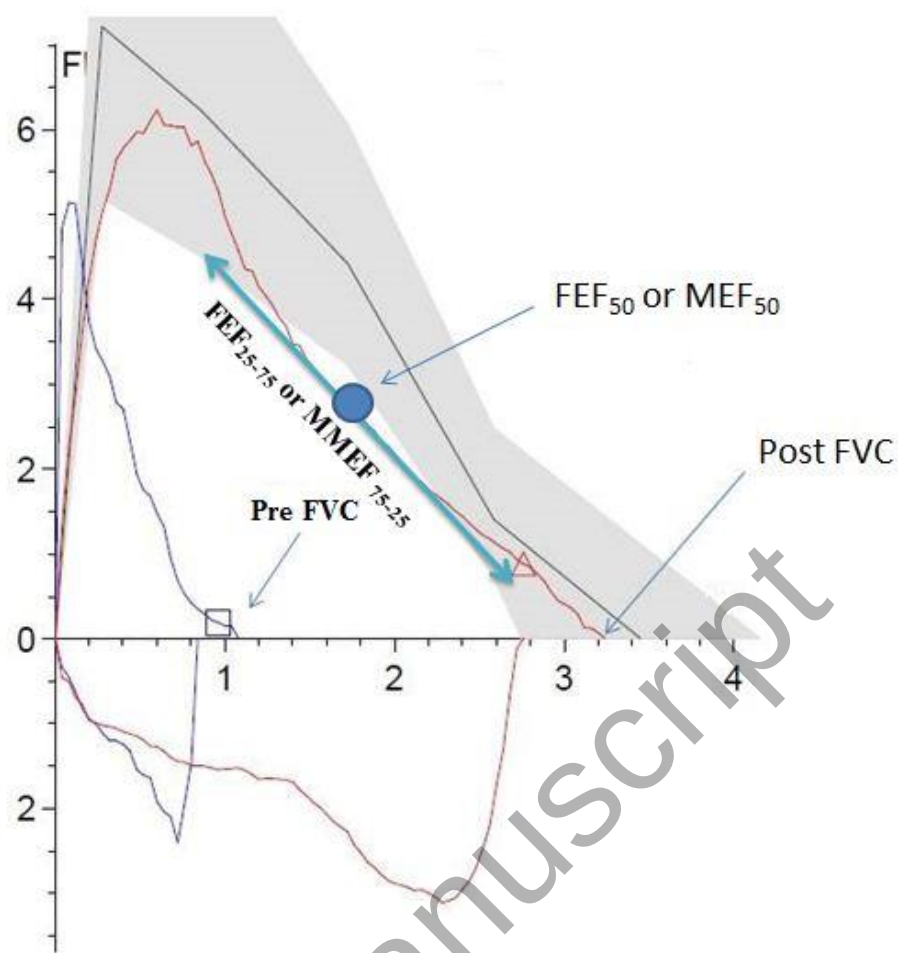


Figure 1. A representative pre-post albuterol and the position of measured and reported values

Table 1. A suggested hierarchy of PFT results and their potential utilization

Test	Percent change or value	Clinical Correlation
FEV ₁	≥ 12% is traditional value	Additional data supports 8% change or greater as highly unlikely in a non-asthmatic ^{10, 13, 14}
FVC	≥ 10% change	Strongly suggests reversed airtrapping ¹⁷
FVC	Low value	Suggests small airway obstruction ¹⁸
FVC	Z score - 1.64 or lower	Lowest 25% of PFT as compared to normals ¹⁷
FEF ₂₅₋₇₅	Below 65% of predicted	Predicts a significant FEV ₁ improvement with bronchodilator ²⁰
FEF ₂₅₋₇₅	≥ 35% improvement	Suggests small airway obstruction ^{10, 18}
FEF50	Low value	Correlates to small air obstruction ¹⁸
MMEF ₇₅₋₂₅	Low value	Same as FEF ^{25, 26}