OFFICE-BASED OBJECTIVE MEASURES IN CHILDHOOD ASTHMA

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Asthma is among the most common chronic childhood diseases affecting 6 million children in the United States.[1] Despite better understanding of the pathogenesis and advances in the treatment of this disease, asthma continues to be a leading cause of school absences, emergency department visits, and hospitalizations in children.[2,3] Although there are many reasons for the substantial morbidity rate associated with asthma, 1 reason stems from the fact that objective monitoring of asthma is not widely performed. The purpose of this review is to provide clinicians with an up-to-date review of the 2 most commonly used office-based lung function measures, peak expiratory flow (PEF) and spirometry, in childhood asthma. In addition, a novel noninvasive measure of inflammation, exhaled nitric oxide, will also be discussed. It is hoped that by increasing the number of tools we have to assess asthma, we can improve the quality of life in patients with asthma, while reducing morbidity and mortality rates.

MEASURES OF LUNG FUNCTION

Because asthma is a disease characterized by airflow limitation, objective monitoring of lung function should be an essential aspect of asthma care. Just as one performs routine blood pressure measures in patients with hypertension, patients with asthma should receive routine pulmonary function monitoring. Lung function measures are useful in establishing the diagnosis of asthma, they provide objective information with respect to the nature, severity, and level of asthma control, and they are useful in assessing response to therapeutic interventions. Last, when used longitudinally lung function tests can track asthma progression over time.

PEF

PEF is a widely used lung function measure because it is easily performed and inexpensive. Although routine PEF monitoring had been strongly encouraged in the past, recent studies have failed to support the benefits of asthma action plans on the basis of PEF monitoring in improving health care utilization. According to the most recent update from the National Heart, Lung, and Blood Institute's (NHLBI) Expert Panel Report for the Diagnosis and Management of Asthma,[2] PEF monitoring is still recommended for patients with moderate to severe asthma and in patients who do not recognize signs and symptoms of worsening asthma. PEF can also be useful early in the evaluation of a child with poorly controlled asthma. In this situation, twice-daily PEF measures can provide an objective means to assess response to pharmacologic intervention. As control is gained, PEF variability and beta-agonist reversibility should decrease as the baseline values rise (Figure 1). Peak flow variability is determined by the following equation: (Morning PEF − Evening PEF)/([Morning PEF + Evening PEF]/2). Once asthma control is optimized, PEF measures can be performed intermittently and at the first sign of asthma worsening.

In summary, the PEF is a useful test, but it has limitations. First, it is an effort-dependent test—a low value can be the result of either a poor effort or worsening asthma. In addition, because it is a measure of large airway function, it is a less sensitive measure of airflow limitation compared with other lung function measures.[4] Last, children with severe asthma can often generate normal or nearly normal PEF values while displaying significantly diminished FEV_1 and FEF_{25-75} values.[5]

Spirometry

Spirometry is the most important lung function test in asthma. With adequate coaching, children as young as 5 years can be taught the maneuver. Spirometry allows for an assessment of flow at several levels of the airway from the large (PEF) to the peripheral airways (FEF_{25-75}). Evaluation of the volume-time curve allows one to assess the adequacy of the child's expiratory effort (Figure 2, *a*). In older children, an acceptable test requires the child to exhale for at least 6 seconds. If a child's expiratory effort is only a

CAMP	Childhood Asthma Management Program	FVC	Forced expiratory volume
eNO	Exhaled nitric oxide	PEF	Peak expiratory flow
FEV_1	Forced expiratory volume in one second		

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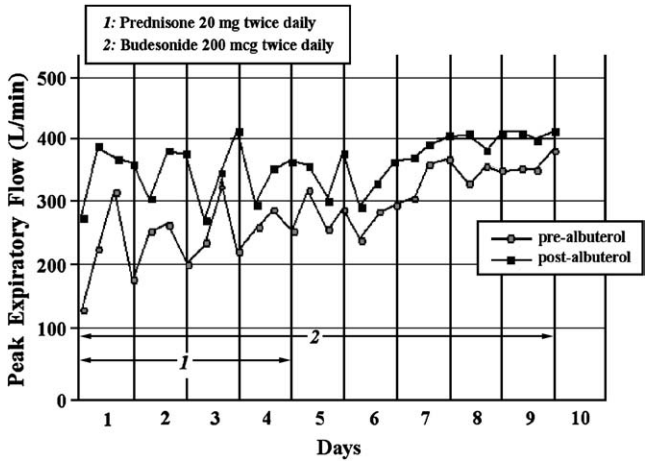

Figure 1. This 12-year old male presented to clinic with poorly controlled asthma requiring albuterol up to 4 times/day. Auscultation of his lungs revealed wheezing on forced expiration, and his FEV_1 was 65% of predicted. He was prescribed prednisone (20 mg twice daily for 4 days) and inhaled budesonide (200 μg twice daily) with instructions to perform PEF measures twice daily as seen in this figure. Note significant diurnal variation in this child's pre-albuterol PEF values and his significant response to albuterol early in his treatment course. Also, note steady improvement in baseline PEFs as his asthma control improved.

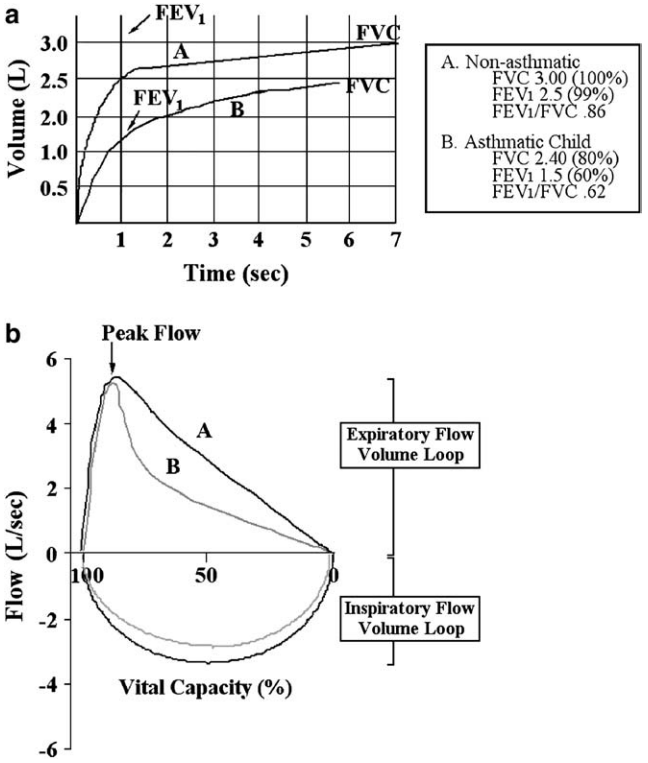

Figure 2. **a**, Volume-time curves from non-asthmatic and asthmatic child demonstrate significant decrease in FEV_1 in asthmatic. Both children's expiratory times are adequate. **b**, Flow-volume curves from same 2 children demonstrating airflow obstruction in asthmatic child with characteristic concave appearing expiratory flow volume loop. Both children have normal inspiratory flow volume loops. Of note, despite diminished FEV_1 and FEV_1/FVC ratio, asthmatic child generated normal PEF.

couple of seconds, the test is unacceptable and the results uninterpretable. An acceptable test in a preschool child is one where there is an obvious peak flow, where there is no sharp drop or cessation in flow, and where there is an exhalation time of greater than 1 second.[6] Evaluation of the flow-volume loop provides information with respect to the degree of airflow limitation. With increasing airflow limitation the expiratory curve becomes more concave or "scooped out" as seen in Figure 2, *b*. The inspiratory flow volume loop should have the appearance of a semicircle. If it has a blunted or scalloped appearance as illustrated in Figure 3, it suggests inappropriate closure of the vocal cords as is seen in vocal cord dysfunction—a masquerader of asthma. The following discussion will provide an overview of the various parameters of value when evaluating a spirometry report.

FEV_1

The FEV_1 is the "gold standard" measure for diseases characterized by airflow limitation[7] such as asthma, cystic fibrosis, and chronic lung disease of prematurity. According to the NHLBI asthma guidelines,[2] patients with mild asthma have FEV_1 values of >80%, those with moderate persistent asthma have values 60% to 80%, while patients with severe persistent asthma have FEV_1 values of less than 60% of predicted.

FEV_1/FVC

The FEV_1/FVC ratio is the amount of air exhaled in the first second divided by all of the air exhaled during a maximal exhalation. The FEV_1/FVC ratio is highest in young children (>90%) and decreases with increasing age.[6] A normal FEV_1/FVC ratio is 86%, with values below 80% indicative of airflow obstruction.[8] Many children with asthma will have FEV_1 values in the normal range while having diminished FEV_1/FVC ratios. In addition, the FEV_1/FVC ratio can provide a better measure of asthma severity compared with the FEV_1 % predicted as recently described.[9]

FEF_{25-75}

The forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) measures airflow in the mid-portion of the vital capacity. It is effort independent and is believed to measure peripheral airway obstruction. The FEF_{25-75} is among the first parameters to be abnormal in pediatric asthma, and it is often the most significantly impaired of all of the spirometric measures.[10] It is the impairment in the FEF_{25-75} that gives the expiratory flow volume curve its characteristic scooped out or concave appearance (Figure 2, *b*). Similar to the FEV_1/FVC ratio, the FEF_{25-75} provides greater sensitivity with respect to lung function impairment in childhood asthma. This was recently demonstrated by Paull et al,[10] who retrospectively analyzed over 24,000 lung function test results in 2728 children with asthma evaluated at a tertiary referral center. They found the mean FEV_1 of the children studied to be well within the normal range at 92.7% of predicted,

with 77% of the values within the normal range (>80% of predicted). In contrast, the mean FEF_{25-75} was only 78% of predicted with only 28% of the FEF_{25-75} values >80% of predicted.

Beta-Agonist Reversibility

Assessment of beta-agonist reversibility is an important aspect of spirometry serving several functions. First, it can aid in the diagnosis of asthma. In a patient with respiratory symptoms consistent with asthma, a positive beta-agonist response (either a 200 mL or ≥12% improvement in FEV_1 after an inhaled beta-agonist) is strongly suggestive of asthma, although patients with cystic fibrosis can also be responsive to beta-agonists. Second, it provides information with respect to reversibility of airflow limitation. Third, beta-agonist reversibility provides information with respect to airway lability and inflammation. This is highlighted by 2 studies published by Covar et al,[11,12] who evaluated the clinical utility of 2 noninvasive measures of airway inflammation, exhaled nitric oxide (eNO) and sputum eosinophils, in children with mild to moderate asthma. The investigators found neither inflammatory measure to correlate with baseline FEV_1, while both correlated with beta-agonist response. Ulrik et al[13] prospectively evaluated asthma progression in a cohort of patients with asthma and found patients with the greatest degree of beta-agonist reversibility at baseline to have the greatest decline in lung function. In addition, these were also at greatest risk of development of fixed airflow obstruction over time.

LUNG FUNCTION IN CHILDREN

What is known and what has yet to be learned?

Most Children with Asthma Do Not Have Chronically Impaired Lung Function

Unlike adults with longstanding asthma where chronic lung function impairment is the norm, children with asthma often have normal lung function during periods of disease stability; yet develop severe airflow obstruction during acute exacerbations.[14] This lability in lung function is likely a reflection of the underlying bronchial hyperresponsiveness that characterizes childhood asthma.[15] That children of all levels of asthma severity will often have normal or nearly normal FEV_1 during periods of stability should come as no surprise because asthma is a slowly progressive disease. Fuhlbrigge et al[16] evaluated the relationship between FEV_1 and risk for a subsequent asthma attack in 3626 children followed up yearly for up to 15 years. The investigators found that less than 1% of the children had FEV_1 values of 60% of predicted or less, whereas 94% had values of 80% of predicted or greater. Of importance, patients with an FEV_1 <60% of predicted had a 70% chance of having an asthma attack in the following year, whereas children with FEV_1 values >80% had only a 25% to 30% chance of having an attack. Additional data come from the Childhood Asthma Management Program (CAMP), which evaluated 1041 children with asthma.[17] Despite the fact that more than 50% of the cohort had moderate persistent asthma on the basis of symptom frequency, the mean pre-bronchodilator FEV_1 was 94% of predicted. Last, Jenkins et al[18] compared the lung function values of children and adults with difficult-to-control asthma and found that despite comparable disease severity, the mean pre-bronchodilator FEV_1 value of the children was 74% of predicted compared to 57% of predicted for adults.

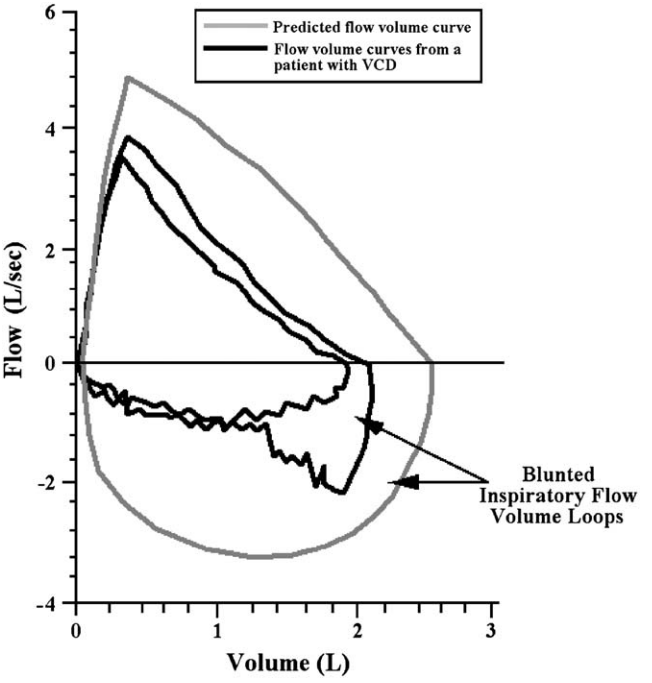

Figure 3. Flow-volume curves from patient with vocal cord dysfunction. This adolescent female presented with recurrent respiratory difficulties refractory to multiple asthma medications. FEV_1 and FVC were equally impaired at 75% of predicted whereas her FEV_1/FVC ratio was normal at 86%. Evaluation of inspiratory flow-volume curve revealed significant blunting caused by inappropriate closure of her vocal cords. She had negative methacholine challenge, which effectively ruled out asthma. She was subsequently diagnosed with vocal cord dysfunction, and speech therapy was begun with eventual resolution of her symptoms.

In summary, the data suggest that a single FEV_1 value is a relatively insensitive measure of asthma severity in children. Thus a normal FEV_1 value should not give one a false sense of security given the inherent airway lability of childhood asthma. On the other hand, if a child's FEV_1 is impaired, asthma therapy should be intensified because that child is not only at risk for having an asthma attack[16] but also at risk for progressive loss of lung function over time.[19]

Are Children with Asthma at Risk for Progressive Loss of Lung Function Over Time?

It is well established that adults with asthma lose lung function at a greater rate than their peers without asthma, with a rate of decline in FEV_1 of approximately 1% of predicted per year.[20] Whether children with asthma also lose lung function at an accelerated rate is less clear. Zeiger et al[21] in a cross-sectional analysis of the children enrolled in the CAMP study found an annual decline of FEV_1 of

0.91% predicted per year of asthma at the time of randomization. This is in contrast to the results presented on completion of the CAMP study, where no decline in the mean pre- or post-bronchodilator FEV_1 was noted after 4 to 6 years of therapy with either budesonide, nedocromil, or placebo.[17]

Although the longitudinal data from the CAMP study failed to demonstrate a reduction in FEV_1, hidden in the mean were patients who had a progressive reduction in lung function over time as reported by Covar et al.[22] These investigators found that approximately one quarter of the children had a >1% per year loss in pre- and post-bronchodilator FEV_1 over the course of the CAMP study. Children at risk for progressive loss of lung function were more likely to be younger, male, to have higher post-bronchodilator FEV_1 values at randomization, and to have had a shorter duration of asthma. Of interest, there was no difference in the percentage of decliners or the slope of the decline in the affected patients treated with active therapy (budesonide or nedocromil) compared with placebo. These data suggest that the process starts early, does not proceed uniformly over time, and may not be altered with currently available therapy.

Further support of the concept of early lung function decline in childhood asthma comes from 3 important birth cohort studies. The Melbourne Asthma Study has followed a large cohort of asthmatic patients from childhood to 42 years of age. Among many important findings, this study was among the first to note that children with persistent asthma already demonstrated a significant reduction in FEV_1 by age 7 to 10 years.[23] In addition, the investigators found that asthma severity tracks over time. Those with severe asthma had the greatest impairment in FEV_1 at the first measurement, and this persisted well into adulthood. The second cohort comes from Dunedin, New Zealand, where Sears et al[24] have followed a large cohort of asthmatics from childhood to adulthood with spirometry performed serially from 9 to 26 years. The investigators found patients with persistent asthma from childhood into adulthood had significantly impaired lung function compared with the non-asthmatic patients, and this difference was already apparent at the initial assessment. The third cohort study comes from Tucson, where Martinez et al[25,26] have followed the lung growth of over 1000 children from 1 year of life to early adulthood. Children with persistent wheezing displayed a progressive decline in lung function from infancy to 6 years compared with children who were "transient," "late onset," and "never" wheezers. In addition, serial lung function evaluation at age 13 years revealed that the steepest decline in FEV_1 among the asthmatic patients studied occurred in the first 6 years of life.

Thus not all children with asthma are at risk of progressive loss of lung function. Identification of children at risk for decline would allow them to be targeted to receive more aggressive therapy with careful monitoring over time in an attempt to halt further progression. In addition, the loss of lung function occurs early in the course of the disease. At present, it is unknown whether any medication or combination of medications will have a protective effect against lung function decline. In 2 other diseases characterized by airflow limitation, chronic obstructive pulmonary disease and cystic fibrosis, no available therapies have been shown to prevent loss of lung function.[27,28]

Are Noninvasive Measures of Airway Inflammation Available?

Asthma is a disease characterized by airway inflammation, yet until recently there were no noninvasive ways to assess inflammation. Over the past decade, a great deal of research has been focused on exhaled nitric oxide. Nitric oxide is a gas produced in large quantities by damaged airway epithelial cells, eosinophils, and macrophages. Many studies have demonstrated its clinical utility in asthma. Several studies have shown eNO to be useful in establishing the diagnosis of asthma,[29,30] whereas other studies have shown eNO levels correlate with both asthma severity and control.[11,31] The eNO has also been shown to predict response to antiinflammatory therapy.[32]

The Niox (Aerocrine, Sweden) system is an eNO analyzer that has recently been approved by the Food and Drug Administration for use in asthma. NO measurement is easier to perform and takes less time than spirometry, with children as young as 4 years able to perform the test. Its major disadvantage at present is the significant cost of the equipment. If the cost of the technology drops significantly, this test could easily be administered in any primary care setting. Studies have shown that it can provide information that is complementary to that obtained by performing spirometry. Obtaining measures of both lung function and airway inflammation, in addition to symptoms and need for rescue beta-agonist use would greatly enhance how we assess asthma severity/control and how we titrate (upward or downward) controller medications.

CONCLUSIONS

Objective monitoring of asthma remains underutilized especially in primary care. Peak flow measurement is often performed due to its ease of use and affordability. Unfortunately, it is relatively insensitive and is no longer recommended for routine home monitoring for many children with asthma. Spirometry remains the "gold standard" lung function test in that provides several different measurements of airflow including the FEV_1, the FEV_1/FVC ratio, and the FEF_{25-75}. It is important to realize that the FEV_1 can be within the normal range during periods of disease stability, but that rapid and significant drops can occur during acute illnesses. The FEV_1/FVC and FEF_{25-75} can provide greater sensitivity compared to the FEV_1 in detecting airflow limitation in children with asthma. As such, these measures should always be assessed when reading a spirometry report. Ideally, spirometry should be performed serially, so that children at risk for progressive loss of lung function can be identified and therapy intensified. Lung function tests provide important information with respect to disease severity and response to therapy. New technologies are emerging that will allow for the assessment of airway inflammation. They have the potential to significantly improve our ability to assess disease activity, especially when the child has normal lung function. Wider application of these

tests will allow for better definition of the natural history of lower airway disease in children over time.

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