

ORIGINAL ARTICLE

Sensitivity of different spirometric tests for detecting airway obstruction in childhood asthmaBenjamin Francisco, PhD, PNP-BC¹, Zarah Ner, MD¹, Bin Ge, MD, MA², John Hewett, PhD², and Peter König, MD, PhD¹¹Department of Child Health, University of Missouri–Columbia, Columbia, MO, USA and ²Medical Research Office, School of Medicine, University of Missouri–Columbia, Columbia, MO, USA**Abstract**

Objective: The objective of this study was to compare different measures of airflow obstruction by spirometry in childhood asthma. The objectives were; (a) to compare sensitivity of large airway tests (FEV₁ and PEFR) with tests at low lung volumes (small airways) (FEF_{25–75}, FEF₅₀ and FEF₇₅); (b) compare within each group which individual tests are more sensitive. **Methods:** This was a retrospective analysis of 2307 spirometry tests performed during outpatient visits on 821 doctor-diagnosed asthma patients aged 6–18. Tests were deemed acceptable if they were acceptable and repeatable by American Thoracic Society (ATS) criteria. **Results:** In mild obstruction, FEV₁ detected 6.8% abnormal tests while FEF₇₅ detected 33% ($p < 0.0001$). In more severe obstruction, the difference was more obvious (FEV₁ 14.8%; FEF₇₅ 71%). Tests at low lung volumes (small airway tests) were also more sensitive than PEFR. Within groups, FEV₁ was more sensitive than PEFR in the large airway tests and FEF₇₅ was more sensitive than FEF_{25–75} and FEF₅₀ among the tests at low lung volumes (small airway tests). The FEV₁/FVC ratio correlated more closely with tests at low lung volumes (small airway tests), than with large airway tests. **Conclusions:** (1) Tests at low lung volumes (small airway tests) are more sensitive than large airway tests; (2) Within groups, the FEV₁ is better than PEFR and FEF₇₅ is better than FEF_{25–75} or FEF₅₀.

Keywords

Asthma in children, pulmonary function testing, sensitivity of tests for obstruction, specificity of tests for obstruction, tests at low lung volumes (small airway obstruction)

History

Received 30 May 2014

Revised 29 October 2014

Accepted 1 November 2014

Published online 25 November 2014

Introduction

Asthma is the most frequent chronic disease in childhood affecting over 10 million children in the US [1].

Management of asthma is complicated by the fact that subjective feeling of patients, i.e. symptoms tend to underestimate the severity of airways obstruction [2–4]. Patient's and parent's recollection of the frequency and severity of symptoms is also unreliable [2]. Physical examination by physicians also underestimates the severity [2]. Therefore, management based on symptoms and doctors examination only, without objective measurements will likely result in under treatment.

Spirometry has been the most widely used measure of lung function. The peak expiratory flow rate (PEFR) has been widely used for home monitoring of lung function and as an office tool in primary care. Finkelstein et al. [5] showed that 75% of primary care physicians used PEFR for the diagnosis or follow-up of asthma, but only 8% used FEV₁ for follow-up and 21% for diagnosis. Among the tests provided by spirometry the forced expiratory volume in one second (FEV₁) has been considered for many years to be the gold standard [6] because it is reproducible and well standardized [7].

However, more recently questions have been raised about FEV₁, being the gold standard for obstruction in children. Evidence began to be presented that FEV₁ can be normal even in children with symptoms of poorly controlled asthma [8–11]. Bacharier et al. [8] found that FVC and FEV₁ did not decrease with severity of asthma, but FEV₁/FVC ratio and FEF₇₅ did. In the CAMP study [10], there was a progressive decline in lung function, but the patients on Budesonide showed a significantly smaller decline on FEV₁/FVC ratio than patients on placebo (0.2% versus 1.8%). FEV₁ did not show a significant difference.

Strunk et al. [11] compared the children from the CAMP study with a group of children without asthma. Children with asthma had significantly lower FEV₁/FVC ratio, but the FEV₁ was only significant in boys, but not in girls. As a result, the latest expert panel report (EPR3) [4], noted that for children the FEV₁/FVC ratio is a more sensitive measure of lung function impairment than FEV₁. Flows at high lung volumes represent caliber of the central (large) airways (FEV₁, PEFR), whereas flows at low lung volumes represent mostly the caliber of peripheral (small) airways (FEF_{25–75}, FEF₅₀, and FEF₇₅) [12,13]. It is not clear if the FEV₁/FVC ratio is a large airway or small airway test.

During a forced expiration, partial obstruction of the peripheral airways profoundly affects the pressure-flow characteristics of the lungs, causing airway collapse to

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occur earlier in time, at a point closer to the alveoli, thus reducing the maximum flow. This is most marked at lung volumes in the lower half of the vital capacity because flow resistance increases as the lung empties. Another reason for the greater sensitivity of spirometric tests at the lower part of the vital capacity is the spatial heterogeneity of airway disease leading to maldistribution of ventilation in diffuse obstructive airway diseases, such as asthma. As a result, the regions of the lung that are more obstructed empty their contents later during expiration, thus resulting in a more exaggerated reduction in expiratory flow at lower lung volumes. Therefore, spirometric tests at the lower part of the vital capacity are considered tests of small (peripheral) airways.

Several studies have shown that small airway tests are more sensitive in detecting obstruction than large airway tests [8–12,14,15]. Some of these studies used tests other than spirometry, such as lung clearance index (LCI), closing volume, closing capacity or multiple breath nitrogen washout, as a small airway test [16,17]. No systematic studies of all the spirometric tests in terms of sensitivity and specificity have been performed.

The premise of this study is that if there is airways obstruction present, that is evidence that the basic process of asthma (inflammation, bronchospasm, etc) are ongoing even if the patient is asymptomatic; therefore, more aggressive treatment is necessary. No attempt was made in our study to correlate airway obstruction with clinical outcomes. Our aim was to show that flows at low lung volumes will frequently show obstruction when the FEV₁ is within the normal range. Many clinicians are still only considering FEV₁ in their interpretation of spirometry. We have seen spirometry interpreted as “normal” with FEV₁ above 80% predicted, when the FEF₇₅ was only 30–40% predicted.

Therefore, it was decided to compare all the spirometrically derived small airway tests (FEF_{25–75}, FEF₅₀, and FEF₇₅) with both large airway tests (FEV₁, PEFR), compare within each group (large and small airway groups) which individual tests are more sensitive.

Materials and methods

This was a retrospective analysis of spirometry results in a Pediatric Pulmonary – Allergy Clinic at the University of Missouri – Columbia. Spirometry was routinely performed at every clinic visit on doctor-diagnosed asthma patients old enough to perform spirometry. Attempts were made from 5 years of age. All tests for the purpose of this study were pre-bronchodilator tests. Tests were deemed acceptable if they were acceptable by ATS criteria and repeatable [7]. Spirometry was performed on a Sensormedics VMAX Encore or Legacy (Sensormedics, Yorba Linda, CA). Predicted normal values for FVC and FEV₁ were based on NHANES data [18]. Predicted normal values for FEF_{25–75}, FEF₅₀ and FEF₇₅ were based on the study by Zapletal et al. [19]. In children under 8 years of age, normal values for FVC and FEV₁ were taken from Wang et al. [20] The normal values from NHANES [18] and Wang [20] are the ones recommended by the ATS/ERS guidelines [21], but they do not have data for FEF₅₀ and FEF₇₅, which are some of the main focus of our study, therefore the Zapletal study [19] needed to be

Table 1. Demographic data of the 821 subjects.

	<i>n</i>	%
Sex		
Male	492	59.93
Female	329	40.07
Race		
Caucasian	684	83.31
African-American	115	14.01
Hispanic	7	0.85
Asian	15	1.83

Age: mean 11.12 years, SD 3.44 years, range 5–19 years.

used. A total of 2307 tests were included between the years 2006 and 2011. More than one test per patient was included; the total number of patients involved was 821. The average number of spirometries per subject was three and the range was 1–39. The mean age and range, sex distribution and race are shown in Table 1. The study was approved by the Institutional Review Board of the University of Missouri – Columbia (#1168298). According to the IRB approval, since the study was retrospective and the data were de-identified, no informed consent was required. We considered FEV₁, and PEFR to be large airway tests and FEF_{25–75}, FEF₅₀, and FEF₇₅ to be tests at low lung volumes (small airway tests) [12,13].

The research questions addressed were:

- (I) Are tests at low lung volumes (small airway tests) more sensitive for detecting obstruction, than large airway tests? [15,22,23].
- (II) Among large airway tests is FEV₁, more sensitive than PEFR and which of the tests at low lung volumes (small airway tests) is most sensitive?

Sensitivity and specificity for each test was determined in two ways:

- (a) By accepting the definition of normal as per the recommendations of the EPR3 guidelines [4], as a FEV₁/FVC ratio >85% and considering only tests defined as obstructed by the ratio. Different degrees of obstruction were defined corresponding to EPR3 [4] for classifying lung function impairment for children with increments of 5% decrements (0.81–85, 76–80, 71–75, 66–70, <66).
- (b) By comparing the number of abnormal tests independent of the FEV₁/FVC ratio.

Normal range was considered PEFR ≥ 80% predicted, FEV₁ ≥ 80% predicted [7,24]; FEF_{25–75} ≥ 70% [25], or ≥ 60% [24,25,26], FEF₅₀ ≥ 70% [27] or 60%. [23]; and FEF₇₅ ≥ 70% or 60% [27].

Statistical analysis

To assess the difference in sensitivity between tests at low lung volumes (small airway tests) and large airway tests as airflow obstruction severity progresses, the McNemar’s tests [28] were performed to compare the percent of obstruction defined by three small airway test (below 70) with the percent of obstruction defined by large airway tests (below 80) for the different level of severities of airflow obstruction defined by FEV₁/FVC ratio ranges (i.e. 81–85%, 76–80%, 71–75%, 66–70%, <66%).

To assess the difference in specificity between the small and large airway tests when the FEV₁/FVC ratio normal (>85%), the McNemar's tests [28] were performed to compare the percent of normal airflow defined by three small airway tests (>70%) with the percent of normal defined by two large airway tests (>80%) for the normal airflow defined by the FEV₁/FVC ratio (>85%).

The McNemar's Tests [28] were also used to assess the difference in sensitivity or specificity among small or large airway tests, respectively.

To assess the association between small or large airway tests and FEV₁/FVC ratio, the correlation coefficients were conducted for each pair and the Williams' (1959) [29] modified version of Hotelling's test was used to compare two overlapping dependent correlations.

To assess the association between small and large airway tests, the correlation coefficient and its corresponding 95% confidence interval was calculated for each pair [30].

These analyses were conducted using SAS 9.2 (Cary, NC). A significance level of 0.05 was used to make the conclusion.

Results

- (I) (A) *By considering only tests showing obstruction on the FEV₁/FVC ratio. Are tests at low lung volumes (small airway tests) more sensitive than large airway tests, as airway obstruction severity progresses?*

Taking FEV₁ as the large airway test for comparison with small airway measures yielded:

At mild obstruction (FEV₁/FVC ratio 81–85) FEV₁ detected 6.8% abnormal tests, while FEF₇₅ detected 33% ($p < 0.0001$), FEF_{25–75} detected 10% ($p = 0.0022$), while FEF₅₀ at 5% abnormal tests was not significantly different from FEV₁. At more severe obstruction, (FEV₁/FVC 76–80) there were 14.8% abnormal tests on FEV₁, compared to 71% on FEF₇₅ ($p = 0.0001$), 42% on FEF_{25–75} ($p = 0.0001$) and 31% on FEF₅₀ ($p = 0.0001$; Figure 1, Table 2). Taking PEFR as the large airway test for comparison yielded somewhat similar results. At mild obstruction (ratio 81–85) PEFR detected 7.9% abnormal tests which was significantly less than the 33% detected by FEF₇₅ ($p = 0.0001$).

However, the difference between PEFR and FEF_{25–75} did not reach statistical significance. PEFR was significantly better ($p = 0.0267$) compared with FEF₅₀ (5% abnormal tests).

Comparison of the specificity of small airway tests and large airway tests when the FEV₁/FVC ratio is normal (>85). Interestingly at normal ratio (>85), there were few abnormal results on any other test, the highest being 5% on FEV₁. The specificity of FEF₇₅ was 97.7% which was significantly better than the 94.5% for FEV₁ ($p = 0.0001$). For FEF_{25–75} the specificity was 98.6%, significantly better than FEV₁ ($p < 0.0001$). The same was true for FEF₅₀, with a specificity of 99.1% ($p < 0.0001$).

- (I) (B) *Comparing the total number of abnormal tests independent of the FEV₁/FVC ratio.*

All tests at low lung volumes (small airway tests) (FEF₇₅, FEF_{25–75}, and FEF₅₀) showed significantly greater ($p < 0.0001$) degree of sensitivity than both large airway tests (FEV₁ and PEFR). FEV₁ had significantly more obstructed tests than PEFR. The FEV₁/FVC ratio had the highest number of obstructed tests (Table 4). The FEF₇₅ detected 50.02% abnormal tests, while the FEV₁ only 20.16% ($p < 0.0001$); however, the FEV₁/FVC ratio detected 75.47% abnormal tests (Table 3).

- (II) (A) *Between large airway tests, how do FEV₁ and PEFR compare in terms of specificity when the FEV₁/FVC ratio is normal (>85%) and in terms of sensitivity when the ratio shows obstruction (<85%).* Specificity for FEV₁ was 94.5% and PEFR 96.5%, $p = 0.0482$. Sensitivity for FEV₁ and PEFR was equal when the obstruction was mild (FEV₁ 81–85%), but FEV₁ was better at all other degrees of obstruction.

- (II) (B) *Comparison between tests at low lung volumes (small airway tests) in terms of specificity when the FEV₁/FVC ratio is normal (>85%) and in terms of sensitivity when the ratio shows obstruction (<85%).* Specificity when FEV₁/FVC ratio is normal was equal between FEF₇₅ and FEF_{25–75} and between FEF₅₀ and FEF_{25–75}, but the specificity of FEF₅₀ at 99.1% was better than FEF₇₅ at 97.7% ($p = 0.0114$). In terms of

Figure 1. Sensitivity of FEV₁ and FEF₇₅ at different levels of airflow obstruction. Differences were statistically significant at the $p < 0.0001$ level, except at FEV₁/FVC ratio <66%.

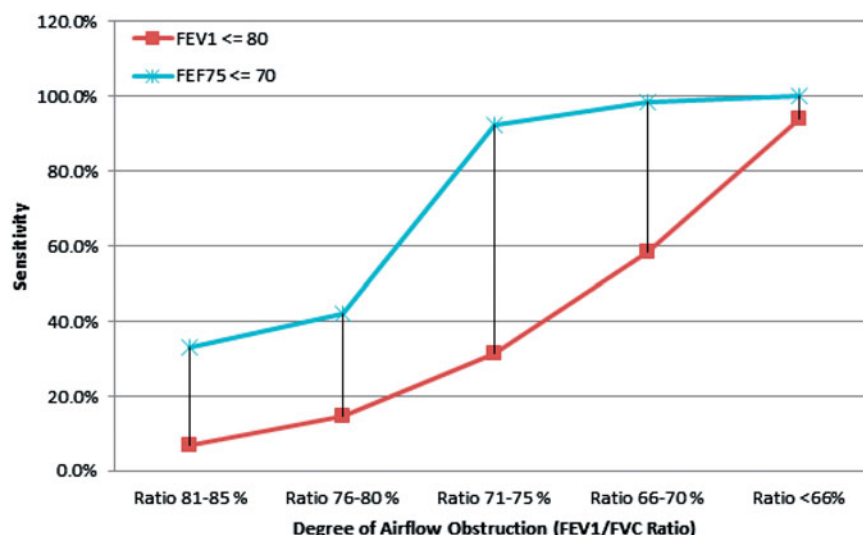


Table 2. Sensitivity of FEV₁ compared to tests at low lung volumes (small airway tests).

Sensitivities at	FEV ₁	FEF ₇₅	FEF ₅₀	FEF _{25–75}
FEV ₁ /FVC 81–85% (<i>n</i> = 633)	6.8% (4.96–9.04%) ^a	33.2 % (29.5–36.9%) ^b <i>p</i> < 0.0001	5.1% (3.48–7.06%) <i>p</i> = 0.0858	10.1% (7.87–12.73%) <i>p</i> = 0.0022
FEV ₁ /FVC 76–80% (<i>n</i> = 528)	14.8% (11.86–18.09%)	71.0% (66.95–74.86%) <i>p</i> < 0.0001	31.1% (29.13–35.2%) <i>p</i> < 0.0001	42.1% (37.8–46.3%) <i>p</i> < 0.0001
FEV ₁ /FVC 71–75% (<i>n</i> = 282)	31.2% (25.84–36.9%)	92.2% (88.43–95.05%) <i>p</i> < 0.0001	73.4% (67.84–78.4%) <i>p</i> < 0.0001	78.7% (73.48–83.3%) <i>p</i> < 0.0001
FEV ₁ /FVC 66–70% (<i>n</i> = 134)	58.2% (49.38–66.6%)	98.5% (94.71–99.82%) <i>p</i> < 0.0001	96.3% (91.51–98.78%) <i>p</i> < 0.0001	95.5% (90.51–98.34%) <i>p</i> < 0.0001

^a(95% confidence limits).^b*p* value compared to FEV₁.

Table 3. Percentage of abnormal tests detected as obstructed by individual parameters.

FEV ₁	PEFR	FEF ₇₅	FEF _{25–75}	FEF ₅₀	FEV ₁ /FVC
20.16% ^{a,b} 0.1852–0.2179%	14.39% 0.1296–0.1582%	50.02% 0.4798–0.5206%	34.98% 0.3302–0.3693%	30.39% 0.2851–0.3226%	75.47% 0.7371–0.7722%

^aComparisons between each test were statistically significant at the level of *p* < 0.0001.^bThe number represents the percentage of obstructed tests from each test, not a percentage of all the obstructed tests.

Table 4. Comparison of the sensitivities of different tests at low lung volumes (small airway tests).

Sensitivities at	FEF ₇₅	FEF ₅₀	FEF _{25–75}	pFEF ₇₅ versus FEF ₅₀	pFEF ₇₅ versus FEF _{25–75}	pFEF ₅₀ versus FEF _{25–75}
FEV ₁ /FVC _{81–85} (<i>n</i> = 633)	33.2% (29.5–36.9%) ^a	5.10% (3.48–7.06%)	10.10% (7.87–12.73%)	<0.0001	<0.0001	<0.0001
FEV ₁ /FVC _{76–80} (<i>n</i> = 528)	71.0% (66.95–74.86%)	31.10% (29.13–35.2%)	42.10% (37.8–46.3%)	<0.0001	<0.0001	<0.0001
FEV ₁ /FVC _{71–75} (<i>n</i> = 282)	92.2% (88.43–95.05%)	73.40% (67.84–78.4%)	78.70% (73.48–83.3%)	<0.0001	<0.0001	<0.0321
FEV ₁ /FVC _{66–70} (<i>n</i> = 134)	98.5% (94.71–99.82%)	96.30% (91.51–98.78%)	95.50% (90.51–98.34%)	=0.1497 (N.S.)	=0.1025 (N.S.)	=0.7055 (N.S.)

^a(95% confidence limits).

sensitivity (Table 4) at ratios of 0.81–0.85%, 0.76–0.80% and 0.71–0.75%, FEF₇₅ was significantly better than FEF₅₀ (*p* < 0.0001) or FEF_{25–75} (*p* < 0.0001) and FEF_{25–75} was significantly better than FEF₅₀ (*p* < 0.0001) but at very severe obstruction (FEV₁/FVC 66–70%) there was no significant difference between the sensitivities (Table 4).

The FEV₁/FVC ratio correlated best with FEF₅₀ with a correlation coefficient of 0.82 as opposed to 0.64 for FEV₁ the difference being significant (*p* < 0.0001). The same is true for PEFR at correlation coefficient of 0.50 (*p* < 0.0001). FEF_{25–75} at correlation coefficient of 0.76 and FEF₇₅ with a correlation coefficient of 0.80, were also significantly more correlated than either FEV₁ or PEFR (Table 5).

We noticed that some patients had a super-normal FVC (>120%).

There were 222 tests with FVC > 120%, of these the ratio of FEV₁/FVC was abnormal (<86) in 175 tests, or 78.8%. On the other hand, FEF₇₅ yielded only 82 (44.7%) abnormal tests among these 175, FEF_{25–75} only 21 tests (12.0%), and the FEF₅₀ only 24 (13.7%) tests. Thus, with a super-normal FVC there are a lot of false-positive tests for obstruction as measured by the FEV₁/FVC ratio.

Table 5. Pearson correlation coefficient between FEV₁/FVC ratio and different spirometry tests.

FEV ₁	PEFR	FEF ₇₅	FEF ₅₀	FEF _{25–75}
0.63*	0.50	0.80	0.82	0.76
0.60 ^a –0.65	0.47–0.53	0.79–0.81	0.81–0.83	0.74–0.77

^a95% confidence limits.**p* values for significance of correlations between each test and FEV₁/FVC ratio were all significant at the *p* < 0.0001 level.

Since some publications recommended defining small airways obstruction as below 60% normal for FEF_{25–75}, FEF₅₀ and FEF₇₅, we analyzed our data for both 70% and 60% as lower limit of normal. We found no differences between findings comparing 70% and 60%. Therefore, only data for 70% as the lower limit of normal are presented.

Discussion

This study demonstrates a higher sensitivity for tests at low lung volumes (small airway tests) compared with large airway tests. This was especially true for FEF₇₅ which detected significantly more obstruction than either FEV₁ or PEFR at

all levels of obstruction. Within groups, FEV₁ was superior to PEFR and FEF₇₅ was better than either FEF₂₅₋₇₅ or FEF₅₀. The FEV₁/FVC ratio correlated better with tests at low lung volumes (small airway tests) than with large airway tests, suggesting that it is perhaps related more closely to flow at low lung volumes but more studies are needed to elucidate this point. To our knowledge, no previous study addressed this correlation.

The importance of measures of small airway flow is supported by findings in this study. The clinical significance of this observation is underscored by many observational and epidemiological studies of asthmatics. In comparing severe to mild to moderate asthma in children, Lang et al. [31] found at pre-bronchodilator spirometry, FEV₁, FEF₂₅₋₇₅ and FEV₁/FVC ratio all showed significant differences between severity groups, but in post-bronchodilator measurements only FEF₂₅₋₇₅ and FEV₁/FVC ratio were significant. Guilbert et al. [32] studied 238 children at high risk for developing asthma who had early life viral wheezing. At 8 years of age they found that those who had rhinovirus infection had lower lung function and FEF₂₅₋₇₅ was better than FEV₁ in showing this relationship. In a review of spirometry results at the Boston Children's Hospital [33], it was concluded that those with normal FEV₁, but abnormal FEV₁/FVC ratio or FEF₂₅₋₇₅, had nearly three times the odds of needing systemic steroid courses and six times the odds for exacerbations. In a comparison of extremely preterm children with their classmates in the United Kingdom [34], the preterm children, tested at 11 years of age had 17% lower FEV₁ and 28% lower FEF₂₅₋₇₅. However, no attempt was made to see if the difference between the tests was statistically significant. Responsiveness of small airway flow to factors known to be important on asthma is also well established. A large amount of evidence shows that FEF₇₅ and FEF₂₅₋₇₅ are more responsive to both adverse environmental exposures and efficacious pharmacotherapy for asthma than are PEFR and FEV₁. Exposure to ozone [35], ambient air pollution [36], and environmental tobacco smoke [37,38] evoked significantly greater decrements in small airway flow compared to large airway flow. In a study of avoidance of dust mites in sensitized children FEF₂₅₋₇₅ was a better predictor of wheezing (by auscultation) and a more sensitive marker of respiratory improvement than FEV₁ or PEFR [39]. Pharmacotherapy trials show substantially greater therapeutic effects on small airway flow than on large airway flow [40-42]. Numerous other studies came to the same conclusion [6,7,13].

Klein et al. [14] studied 91 children with moderate to severe asthma. They measured PEFR, FEV₁, and FEF₂₅₋₇₅. Their findings are in agreement with our findings in terms of the FEF₂₅₋₇₅ being the most sensitive test (53% abnormal tests) compared to 18% by FEV₁ and 27% by PEFR. Their findings differed from ours by showing the PEFR to be more sensitive than FEV₁. However, it is difficult to compare these two studies, because they considered obstruction values of less than 80% of personal best for all three tests, while in our study obstruction was defined as less than 80% of predicted normal for FEV₁ and PEFR and less than 70% for FEF₂₅₋₇₅. Ferguson [25] also found the PEFR more sensitive than FEV₁, but they used the mini-Wright peak flow meter at home, and

considered abnormal values for it below 75% for percent predicted or personal best. Bernardino et al. [43] found no difference between PEFR and FEV₁. On the other hand, Van Dalen et al. [44] showed the FEV₁ was significantly different between asthmatics and normal controls, while PEFR was not.

Several studies showed greater sensitivity to FEF₇₅ than FEF₂₅₋₇₅ but there was no statistical analysis to determine if the difference was statistically significant. Thus, Gao et al. [36] studied 2060 school children in Hong Kong and showed that districts with high pollution compared with those with low pollution had a 7.6% lower FEF₂₅₋₇₅ but 8.4% lower FEF₇₅ in boys. Gilliland et al. [37] examined 3357 school children in order to evaluate the effect of in utero smoke exposure. They found lower FEF₂₅₋₇₅ by 4.6% and FEF₇₅ by 6.2% in those exposed.

When the data were analyzed independent of considering the FEV₁/FVC ratio as the gold standard, it also showed somewhat similar results with the analysis considering the ratio as the gold standard of obstruction. The tests at low lung volumes (small airway tests) were more sensitive than the large airway tests, the FEF₇₅ was the most sensitive small airway test and the FEV₁ was better than the PEFR.

The FEV₁/FVC ratio did show the largest number of obstructed tests. However, in almost 10% of tests (9.6%), when the FVC was super-normal, the ratio showed a lot of false-positive tests of obstruction. In those cases, the FEF₇₅ was helpful in detecting real obstruction.

Most research questions addressed in this study arose directly from challenges encountered interpreting spirometry in the care of children with asthma. Of particular interest is the fact that some clinicians doubt the usefulness of tests at low lung volumes (small airway tests) and do not use an interpretive approach that considers both large and small airflow obstruction.

Percent predicted peak flow (or peak flow rate) is widely used in asthma care, yet this parameter demonstrates the lowest sensitivity to airflow obstruction. Percent predicted FEV₁ is significantly more sensitive than PEFR at all levels of obstruction except mild, when neither PEFR nor FEV₁ is useful.

In 2007, a greater emphasis by EPR3 [4] on assessing FEV₁/FVC ratio prompted careful comparison of ratio and FEF₇₅. We recognized that these two parameters were closely associated and very useful in assessing the clinical course of asthma. However, ratio and FEF₇₅ were not always in agreement. A particular condition under which disagreement was common occurred in the subgroup of supernormal FVC (>120% predicted) tests where low ratio often was not accompanied by low FEF₇₅. Approximately 10% of all tests (222) performed in this study resulted in an FVC > 120% of predicted. An unusually high percentage (79%) of these supernormal tests were abnormal for FEV₁/FVC ratio. However, most supernormal FVC tests were found to be normal with 55% by FEF₇₅ and 88% by FEF₂₅₋₇₅. About half of the patients with super-normal FVC had such tests more than on one occasion. These findings argue against a determination of airflow obstruction for tests with FVC > 120% predicted, ratio < 0.86 and normal FEF₇₅ or FEF₂₅₋₇₅. Additional studies are needed to clarify guidelines for interpreting spirometry for supernormal FVC tests. The

FEV₁/FVC ratio can be sometimes spuriously elevated if the patient does not exhale completely. This would also affect the FEF_{25–75}, FEF₅₀ and FEF₇₅ which would be spuriously high. However, incomplete exhalation can be usually detected by following the expiration time and the expiratory flow plateau.

For many years the argument against wider use of small airway tests was their less good reproducibility than that of FEV₁. Thus, Nickerson et al. [45] found that in normal subjects, the coefficient of variation (CV) was 3.6 for FEV₁, 5.5 for FEF_{25–75}, 6.1 for FEF₅₀ and 8.4 for FEF₇₅. In cystic fibrosis patients the variability was higher, but they did not include asthma patients in their study. Cochrane et al. [46] found a CV of 2.9% for FEV₁ and 8.2 for FEF₇₅ in normal adults. Nevertheless, they concluded that even though the FEV₁ was more suitable for cross-sectional screening the small airway tests being more sensitive would be more useful for long-term studies when the onset of disease is sought.

The strengths of our study are that it compared all three tests at low lung volumes (small airway tests) (FEF₇₅, FEF_{25–75}, and FEF₅₀) with both large airway tests (FEV₁ and PEF_R) in terms of their sensitivity and demonstrated that there are statistically significant differences. Previous studies compared only some of these tests and no attempts were made to show if differences were statistically significant. To our knowledge, this is the first analysis of the relationship between FEV₁/FVC ratio with large versus small airway tests. Weaknesses of our study are that we could not evaluate the reproducibility of these tests, and it was a cross-sectional study instead of a longitudinal one. The designation of FEV₁ as large airway test and the FEF_{25–75}, FEF₅₀ and FEF₇₅ as small airway tests is mostly correct, but it is not an absolute separation, since FEV₁ can also be affected by small airways in severe obstruction.

Our study strongly supports use of tests at low lung volumes (small airway tests) for clinical management of asthma. Because of their markedly greater sensitivity they deserve a second look as outcome measures in interventional studies such as drug trials in asthma, but more trials are needed for this indication. Tests at low lung volumes (small airway tests) also have the advantage of being more effort-independent, than FEV₁ and PEF_R. However, no single test can replace all the other tests for evaluating different aspects of this complex disease.

Conclusion

In conclusion, tests at low lung volumes (small airway tests), especially FEF₇₅ are more sensitive than FEV₁ and should be considered in the clinical management of childhood asthma. This would result in earlier detection of obstruction and better clinical outcomes.

Acknowledgements

The authors wish to thank Ms. Erin Jackson for typing the manuscript and Jennifer Andert BHS, RRT-NPS, and Mark Shiner BSOE, RRT, for helping with the data collection. Mr. Shiner also helped with normal spirometric test equations. Ms. Cynthia Haydon, BA, Senior Grant Writer, School of Medicine helped to edit the manuscript.

Declaration of interest

The authors have no financial, consulting or personal relationships with other people or organizations that could influence (bias) the authors' work. Financial support was used from local funds from previous projects.

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