Forced expiratory decay in asthmatic preschool children – Is it adult type?

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Summary
Background: The forced expiratory decay in healthy preschool children portrays a convex shape that differs from the linear decay in the older healthy population. The “adult-type” expiratory decay during airway obstruction is concave. The study objective was to determine if the expiratory decay in young asthmatic children is “adult-type”.

Methods: Among 245 children (age 3–7 yrs), 178 had asthma (asthmatics) and 67 were non-asthmatic (controls). The expiratory flow decay was inspected by FEF25-75/FVC ratio (Z1.0 when linear). Values were compared to those of our formerly studied (n=108) healthy children. A meaningful obstruction in FEF25-75/FVC ratio was defined as 2-zScores from healthy. A meaningful response to bronchodilators was related to non-asthmatics.

Results: In healthy subjects FEF25-75/FVC ratio declined with age from 1.73 ± 0.17 to 1.28 ± 0.11. Non-asthmatics portrayed ratio values similar to those of healthy subjects. In asthmatics, 118/178 displayed a convex to linear expiratory decay (FEF25-75/FVC Z1.33 ± 0.22). Sixty/178 asthmatics portrayed concavity (FEF25-75/FVC-0.79 ± 0.16) that appeared when FEF50 was 43.4 ± 12%healthy. Concavity appearance was also age-dependent (30.4% of 3–4 y old and 59.1% of 6–7 y). Vital-Capacity decreased in either decays, forming a visually petit curve. Most asthmatic children respond to bronchodilators by a meaningful elevation in FEF25-75/FVC values and by a visual change in the shape of the curve. Other common spirometry indices also increased meaningfully.

Conclusion: Most asthmatic preschool children portray convex to linear expiratory decay with diminished vital-capacity, resulting in a visually smaller than healthy curve, with seemingly

Abbreviation list: FVC, forced vital capacity; FEVt, forced expiratory volume at t seconds; PEF, peak expiratory flow; FEF25-75, forced expiratory flow at 25–75%FVC; FEF50, forced expiratory flow at 50%FVC.

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normal expiratory decay. These curves may be misinterpreted as “normal” or as “no-cooperation” and may lead to misinterpretation. In response to bronchodilators, FEF25-75/FVC value increases in asthmatics and the curve changes from concave to linear or from linear to convex contour.

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Introduction

Spirometry is a simple technique that describes airway obstruction in relation to lung volume and is a basic tool used for the diagnosis, classification, and management of a variety of pulmonary diseases in the general population (age >6 years). Despite recent advances in techniques, suitable adaptations for age, and the existence of reference values in the preschool age,1–3 the clinical significance of spirometry has often been questioned. Poor cooperation on the child’s part and lack of recommendations for identifying airway obstruction or response to bronchodilators by the common guidelines have often been raised as probable reasons for the limited use of spirometry.4

Airway anatomical and physiological differences between the younger and older populations may also contribute to difficulties in interpreting spirometry in the preschool age. In the general healthy population, the expiratory decay of the flow/volume is linear (“adult type”).5,6 In healthy preschool children the expiratory decay portrays a convex shape.7,8 The convex shape is caused by the high flow derived from fully developed airways relative to small lung volumes caused by incomplete alveolarization in those young children.9–14 During airway obstruction in adults the expiratory decay becomes concave.5,6 This concavity is a reflection of the proportionally greater reduction in mid-vital capacity flows than reduction of the FVC.5,6 The importance of detecting concavity was underlined by the ATS/ERS guidelines.15 FEF25-75/FVC ratio can be used as a surrogate measure of airway size relative to lung size.6 When FEF25-75/FVC equals > 1.0 the decay is linear, as found in the healthy general population.6 During airway obstruction when the curve becomes concave, the FEF25-75/FVC ratio decreases below 1.0.14,16 The study aims to define if the expiratory decay contour in asthmatic preschool children is concave by assessing FEF25-75/FVC ratio.

Subjects and methods

The study was approved by the local ethics committee of the Rambam Health Care Campus (Institutional Review Board 0304-11-RambamMC). Children participating in the study were 3.0–7.0-years-old and included asthmatic and non-asthmatic children. Data were collected retrospectively during 2011.

Children with Known Asthma (Asthmatics) included children who were defined as asthmatics according to GINA guidelines,17 who suffered from frequent episodes of wheezing, activity-induced cough/wheeze, nocturnal cough without viral infections, and absence of seasonal variations. All these children had a previous positive methacholine/exercise challenge test or response to bronchodilators.18,19

Non-Asthmatics — included children who were referred to the Pediatric Pulmonary Unit at Meyer Children’s Hospital because of non-organic cough or sigh to exclude asthma. This group included children who had no previous treatment for asthma, no family history of asthma, and no hospitalization due to asthma attack. On previous visits these children had negative methacholine or exercise challenge tests, with no response to bronchodilators.

Exclusion criteria for all children were the inability to comply with repetitive reliable simple spirometry or any chronic respiratory illness except for asthma.

Spirometry measurements

Spirometry maneuvers were performed using a commercial spirometer (KoKo-Dosimeter, nSpire Healthcare Inc, Longmont, CO, USA). Tests were performed by a highly trained technician, aided by incentives that included targets for peak flow and vital capacity, and were performed in the standing position without a nose clip. Each test included at least three technically acceptable curves.7 The technical acceptance of spirometry data was inspected in relation to recommendations for the preschool age.5 The single best FVC + FEV1 (or FVC + FEV0.5) curves were stored for further analysis, where common spirometric indices values were inspected. Reproducibility was assessed as the difference between the best and the second best curve values.

Initial FEF25-75/FVC ratios were calculated, where values above 1.0 were considered convex and below 1.0 as concave. FEF25-75/FVC ratio data from healthy preschool children formerly studied4 were evaluated in relation to the annual age. The significance of the deviation of FEF25-75/FVC ratio and other common spirometry indices from healthy were calculated by unpaired-t test. Correlations were sought between several spirometry indices (%healthy) and FEF25-75/FVC ratio.

We also wanted to assess the change in the curve contour in response to bronchodilators; therefore flow/volume maneuvers were repeated 15 min after inhalation of 2 puffs of 100 mg Albuterol via a volumetric spacer. Changes in expiratory decay contour in response to bronchodilators in the asthmatic and non-asthmatic children were analyzed by comparing the baseline values of FEF25-75/FVC ratio to the post-bronchodilator values by paired t-tests. A meaningful change in FEF25-75/FVC ratio was defined as a change of >2-zscores (in relation to non-asthmatics). Data are presented as mean ± standard deviation (SD) unless otherwise indicated. p < 0.05 was considered significant.
Results

We inspected spirometry data from 260 (107 female) children; 67 were non-asthmatic and 193 were asthmatic. Data from 15/193 asthmatic children were suspected of non-cooperation since their initial FEF25-75/FVC was equal to or higher than the ratio of healthy/per-age group and their spirometry did not meet acceptability criteria. Therefore data analysis included 178/193 asthmatic children. Children were similar in height and weight in both groups. The mean age of all children (n = 245) was 4.8 ± 1.1 yrs; the age composition was: <4.0 years n = 59 (11 of them <3.0 yrs); between 4 and 5 years n = 73, between 5 and 6 years n = 72, and between 6 and 7 years n = 41. The mean height was 109 ± 9 cm and weight 19.1 ± 3.8 kg.

Baseline spirometry

The difference between two replicates of baseline measurements ranged between a minimum of 3.3 ± 2.4% for FEV0.5 to a maximal value of 8.0 ± 6.8% for FEF25-75 for all 245 children. The baseline spirometry common indices values are presented in Table 1 for both asthmatic and non-asthmatic children in relation to healthy. Non-asthmatics had spirometry values within the healthy range for each of the indices. The asthmatic children had spirometry indices significantly lower than healthy and non-asthmatics.

Determination of concavity

In healthy children FEF25-75/FVC ratio differences between two replicates was 5.9 ± 9.3% for all ages. The FEF25-75/FVC ratio values declined with age from 1.73 ± 0.17 when children were younger than 4 y to 1.5 ± 0.18 between ages 4 and 5, to 1.46 ± 0.17 between 5 and 6, and 1.28 ± 0.11 >6.0 years of age. A similar decrease with age in FEF25-75/FVC values was found in our non-asthmatics, where values decreased from 1.68 ± 0.08 when children were younger than 4 y to 1.60 ± 0.06 between ages 4 and 5, 1.55 ± 0.04 between 5 and 6, and 1.32 ± 0.06 >6.0 years of age.

In 118/178 (66%) asthmatic children FEF25-75/FVC was ≥1.0, displaying a convex to linear expiratory decay and only 60 (34%) asthmatic children showed a concave expiratory decay (FEF25-75/FVC <1.0). The spirometry values of the asthmatics are presented in Table 2. FVC, FEV0.5, and FEV1 were similar regardless of expiratory contour. FVC was decreased (<-10%healthy) in 105/118 children with convex to linear decay and in 43/60 children having concave expiratory decay. Children presenting a concave curve had significantly more reduced mid-flows compared to asthmatic children having a convex or linear decay.

An example of scanned flow volume curves is presented in Fig. 1, showing baseline contour in relation to healthy and change in response to bronchodilators.

No correlation was found between FEV1 (%healthy) and the expiratory decay contour. The relation between FEF50 (%healthy) and FEF25-75/FVC ratio is presented for the asthmatics in Fig. 2. A vertical line at FEF25-75/FVC = 1.0 presents the change from convex to concave expiratory decay. FEF50 in the figure represents the small airways since FEF25-75 is part of the FEF25-75/FVC ratio evaluated.

Table 1 Baseline lung function (%healthy) in non-asthmatics and asthmatics.

<table>
<thead>
<tr>
<th>Spirometric index</th>
<th>Non-asthmatics</th>
<th>Asthmatics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 67</td>
<td>N = 178</td>
</tr>
<tr>
<td>FVC</td>
<td>95 ± 7</td>
<td>71 ± 14</td>
</tr>
<tr>
<td>FEV0.5</td>
<td>100 ± 10</td>
<td>68 ± 15</td>
</tr>
<tr>
<td>FEV1</td>
<td>103 ± 9</td>
<td>73 ± 14</td>
</tr>
<tr>
<td>PEF</td>
<td>97 ± 9</td>
<td>69 ± 14</td>
</tr>
<tr>
<td>FEF25-75</td>
<td>96 ± 16</td>
<td>53 ± 16</td>
</tr>
<tr>
<td>FEF50</td>
<td>97 ± 15</td>
<td>57 ± 19</td>
</tr>
<tr>
<td>FEF25-75/FVC ratio</td>
<td>1.55 ± 0.27</td>
<td>1.17 ± 0.34</td>
</tr>
</tbody>
</table>

The effect of age on the appearance of a concave decay is presented in Fig. 3. The appearance of concavity at age 3–4 years was 30.4% that of the 3-year-old children and increased to 59.1% when children reached the age of 6–7 years.

Changes in expiratory curve in response to bronchodilators

The non-asthmatics group showed insignificant changes in common spirometry indices from baseline values in response to bronchodilators: FVC changed by 1.2 ± 6.1%, FEV0.5 by 0.6 ± 4.30%, FEV1 by 0.6 ± 4.7%, PEF by 0.6 ± 6.7%, FEF25-75 by 2.6 ± 6.9%, and FEF25-75/FVC ratio changed by 2.8 ± 10.8%. A meaningful change of >2zScores was equal to a change %baseline of >11%, 9.2%, 10.0%, 14.0%, 16.4%, and 24.4%, respectively, for these parameters. The median increase in FEF25-75/FVC ratio among the asthmatic children with initial concave curve was 48.2% (95% CI 45.2–67.2%) and among the children having initial convex to linear expiratory decay 32.2% (95% CI 29.9–38.8%; p < 0.0001). The proportion (%) of asthmatic children responding by >2zScores, in relation non-asthmatics, to bronchodilators in the various spirometry indices is presented in Table 3.

Discussion

The important point in this paper is that significant intrathoracic airway obstruction can be present without an

Table 2 Baseline lung function in asthmatics according to expiratory decay.

<table>
<thead>
<tr>
<th>Spirometric index</th>
<th>Convex/linear decay</th>
<th>Concave decay</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 118</td>
<td>N = 60</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>72 ± 13</td>
<td>77 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>FEV0.5</td>
<td>72 ± 14</td>
<td>69 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1</td>
<td>78 ± 15</td>
<td>77 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>PEF</td>
<td>68 ± 15</td>
<td>61 ± 15</td>
<td>0.0036</td>
</tr>
<tr>
<td>FEF25-75</td>
<td>60 ± 14</td>
<td>40 ± 9</td>
<td>0.0001</td>
</tr>
<tr>
<td>FEF50</td>
<td>63 ± 16</td>
<td>44 ± 14</td>
<td>0.0001</td>
</tr>
<tr>
<td>FEF25-75/FVC ratio</td>
<td>1.33 ± 0.22</td>
<td>0.79 ± 0.16</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
obviously abnormal “adult type” flow-volume curve configuration. From age 3 though 7 years, the human lung undergoes dramatic growth which is not proportionate. Because normal values change rather significantly during this period, spirometric interpretation must be very careful with detailed awareness of the changing normal values. These norms are not just reflected in numbers but in the configuration of the flow-volume curve.

In the present study we aimed to define the deviation of the preschool spirometry configuration from the “adult type” curve, by describing the expiratory decay contour in asthmatic preschool children. Our data showed that most preschool asthmatic children portray a convex to linear decay of the expiratory limb accompanied by a reduction in vital capacity. The common “adult type” concave expiratory curve appeared more when children were six years of age or alternatively when mid-expiratory flows were severely reduced compared to healthy. Thus, the flow volume curve of a young preschool child with "mild to moderate" obstruction differs fundamentally from the concave adult type curve and could be misinterpreted by visual inspection as a seemingly normal curve. Severely obstructed airways may be presented by a “petit” flow/volume curve accompanied by convex to concave decay that could very easily be visually misjudged as non-cooperation. Yet both shapes of curves change in response to bronchodilators toward linearity or convexity (depending on the initial shape) and by an elevation $>2z$Scores from non-asthmatics in the common spirometry indices, regardless of initial expiratory decay.

We found that 66% of our asthmatic children did not display a concave expiratory decay. In the search for concavity during airway obstruction in the preschool asthmatic children, Neve et al. used the FEF50/PEF ratio. They found that 73% of their wheezy children with normal or mild obstruction according to guidelines had “normal” FEF50/PEF values, i.e., did not present concavity. Despite the absence of concavity, FEF25-75/FVC ratio was significantly lower than in healthy controls, insinuating that it may be essential to relate flows to lung volume in this age group.

We found that in the asthmatic preschool children a reduction in FVC may play a major role in maintaining FEF25-75/FVC ratio $\geq 1.0$. The decrease in vital capacity may be due to premature airway closure of peripheral airways and air trapping that may occur even with mild obstruction. This may cause an increase in functional residual capacity (FRC), which leads to breathing at higher levels of the pressure/volume curve to ease ventilation. Elevation of residual volume in asthmatics was shown to correlate with both peripheral airway resistance and the degree of air trapping assessed by high resolution CT scan. Forced vital capacity (FVC) has been shown to inversely correlate with RV/TLC, indicating that reduction in FVC may suggest air trapping that should be confirmed by lung volume measurements. In the present study we did not measure FRC, yet in an earlier study from our group we found a good correlation between the rise in FRC and the decrease in VC in relation to airway obstruction measured after a methacholine challenge test. The finding that peak expiratory flows (PEF) were also reduced in most of the children is strengthened by Eid et al., who showed that changes in PEF may occur alongside a decrease in FVC in children. All these findings emphasize that a reduction in FVC does not necessarily indicate poor cooperation.

Once FEF50 was significantly decreased from healthy (<43.4 ± 12% healthy FEF50), the “adult type” concavity was more apparent. These findings are in agreement with
Neve et al.\textsuperscript{7} who found that MEF50%/PEF ratios were lower than those of healthy children in their asthmatic children with moderate to severe obstruction. Additionally, we found an effect of age on the appearance of a concave decay; i.e., concavity appeared more in the six-year-old children than in younger ones as FEF25-75/FVC ratio approached 1.0. The age-related concavity of the curve was strengthened by the findings that 43% of asthmatic school children show a concave-shaped flow-volume curve in baseline lung function studies.\textsuperscript{23}

The effect of bronchodilators on the flow/volume ratio was also inspected. For that purpose we recruited data from pre-selected non-asthmatics to avoid inadvertent inclusion of asthmatic subjects. Their baseline FEF25-75/FVC values were similar to those of a larger group of healthy children in relation to age, and their response to bronchodilators was minimal. We found that asthmatic children with either convex to linear expiratory decay or with concave decay responded to bronchodilators. FEF25-75/FVC elevation was accompanied by a significant increase in most spirometry indices. Interestingly, FVC also increased significantly in more than half of our tested asthmatic children, while this parameter is not considered a parameter for response to bronchodilators in the older population.\textsuperscript{15} These findings emphasize that a small curve with linear expiratory decay may indeed present airway obstruction.

These findings are in agreement with earlier studies showing that children with severely obstructed airways may have hyperinflation, and that FRC may decrease after bronchodilator inhalation, allowing an increase in FVC.\textsuperscript{24–29} Similarly to young children, it has been shown that older asthmatics may decrease their lung function by showing a concavity in the flow volume curves and/or by shifting the curve to an identical “smaller” one (decrease in FVC).\textsuperscript{30}

**Study limitations:** Dealing with this age group, it is crucial to have full cooperation with flow/volume maneuvers. Indeed, one could claim repeatable “no cooperation” curves. In our study we followed all recommendations for technically correct flow volume maneuvers. Further, the findings were consistently spread throughout all severity levels of airway obstruction; way beyond the proportion of “no cooperation” known in the literature.\textsuperscript{1} The regression in peak expiratory flow along with FVC strengthens our assumption that “petit curves” with linear regression are genuine.

In this study we determined concavity by the FEF25-75/FVC ratio index when linear, although FEF25-75 itself depends on FVC and if the FVC is not adequate, the ratio will rise by definition. Whereas the index is not standardized, the definition of concavity by -2-zScores from healthy values were similar to those of a larger group of healthy children in relation to age, and their response to bronchodilators was minimal. We found that asthmatic children with either convex to linear expiratory decay or with concave decay responded to bronchodilators. FEF25-75/FVC elevation was accompanied by a significant increase in most spirometry indices. Interestingly, FVC also increased significantly in more than half of our tested asthmatic children, while this parameter is not considered a parameter for response to bronchodilators in the older population.\textsuperscript{15} These findings emphasize that a small curve with linear expiratory decay may indeed present airway obstruction.

**Conclusion:** This study indicates that the obstructed flow volume curve contour in the asthmatic preschool age may differ fundamentally from that of adults by being smaller and having convex to linear shape. The findings insinuate that caution should be taken not to misinterpret such displays as “normal” if mildly obstructed or non-cooperation if severely obstructed. Most asthmatic children respond to bronchodilators as indicated by reversibility in the shape of the curve. Further studies on lung volumes during obstruction and dilation are needed to support the findings of this study.

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**Author contribution and conflict of interest statement**

1. Dr. Daphna Vilozni is the senior author of this manuscript, had substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and in the final approval of the version to be published. Dr. Vilozni has no conflicts of interest to disclose.

2. Dr. Fahed Hakim was thoroughly involved in patient recruitment and performing the physical examinations of the children, and in the interpretation of pulmonary function data. Dr. Hakim has no conflicts of interest to disclose.

3. Dr. Galit Livnat was thoroughly involved in patient recruitment and performing the physical examinations of the children, and in the interpretation of pulmonary function data. Dr. Livnat has no conflicts of interest to disclose.
4. Prof. Lea Bentur is the senior author of this manuscript, had substantial contributions to conception and design, interpretation of data and in the final approval. Prof. Bentur has no conflicts of interest to disclose.

References


