Bronchodilator responsiveness using spirometry in healthy and asthmatic preschool children

Luis Miguel Borrego,1,4 Janet Stocks,2 Isabel Almeida,1 Sanja Stanojevic,2,3 João Antunes,1 Paula Leiria-Pinto,1 José E Rosado-Pinto,1 Ah-Fong Hoo2

ABSTRACT

Objective To assess repeatability and reproducibility of spirometry measurements, and bronchodilator responsiveness (BDR), in healthy 3–6-year-old preschool children and those with asthma.

Design Spirometry was performed before and 20 minutes after administering either inhaled placebo (for repeatability) or 400 μg salbutamol (for BDR) on two separate occasions (reproducibility) 3–23 days apart in asthmatic preschoolers and healthy controls.

Settings Lung Function Laboratory, Hospital de Dona Estefania, Lisbon.

Participants Healthy preschool children and those with physician-diagnosed asthma, recruited from local Health Clinics and Outpatient Clinic.

Main outcome measures Paired measurements of forced expired volume in 0.75 s (FEV0.75) and forced mid-expiratory flows (FEF25–75).

Results Technically successful baseline results were obtained in 86% of children assessed. Paired data were obtained in 43 asthmatic and 22 controls (median (range) age: 5.1 (3.4–6.8) years). Baseline FEV0.75 was significantly lower in asthmatic children (mean (SD): 90 (15)% predicted) than in controls (102 (13)% predicted; p<0.001). Within-occasion coefficient of repeatability following placebo was similar in both groups, being 10.4% in asthma and 13.2% in controls for FEV0.75. Following bronchodilator, FEV0.75 increased significantly more in asthmatic preschoolers (mean (SD): 15.0 (12)%) than in controls (4.5 (5)%; p<0.001), with no significant difference between groups post-bronchodilator. Between-occasion variability was similar to within-day repeatability in controls, but almost twice as high in asthmatic children.

Conclusions BDR can be assessed reliably using FEV0.75 in wheezy preschoolers, provided within-subject variability and responsiveness in health are taken into consideration.

INTRODUCTION

The prevalence of asthma varies with 4.1%−26.7% of Western European preschool children (aged 5–6 years) being affected (9.6% in Portugal).1 Many children with recurrent wheeze tend to outgrow their symptoms, whereas others wheeze persistently throughout adulthood. The diagnosis and treatment of asthma in young children may be challenging to the clinician2–4 and mild intermittent asthma is often misdiagnosed.2–4,6–7 Since clinical symptoms alone may be insufficient for diagnosis, more objective assessments of airway obstruction have been recommended.8

In older subjects, pulmonary function tests (PFTs) are an integral part of the management of respiratory disease contributing towards diagnosis, prognosis, monitoring of disease evolution and evaluating effects of therapeutic interventions. During recent years, it has been shown that most preschool children (preschoolers) can also perform these tests if adequately motivated and supervised.9–12 American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines8 and improved reference equations for such tests are now available for this age group.13

Standardised measurements of bronchodilator responsiveness (BDR) using spirometry are well established for older subjects, a positive response usually being defined when forced expired volume in 1 s (FEV1) increases by at least 12% and 200 ml,14–17 but the extent to which this applies to young children remains unclear.3,8

Despite increasing use of PFTs in preschoolers to assess both baseline values and bronchial responsiveness, interpretation of results in this age group is often limited by the lack of knowledge regarding within- and between-occasion variability3,8 and the extent to which healthy children of similar age respond to bronchodilators.10–21

What is already known on this topic

▸ Spirometric assessment of bronchodilator responsiveness is important when diagnosing asthma but its usefulness in preschool children has yet to be established.

▸ Recent introduction of guidelines and quality control criteria for preschool children have facilitated accurate assessments of spirometry in children as young as 3 years of age.

What this study adds

▸ This study demonstrates that in wheezy preschool children (aged 3–6 years), bronchodilator responsiveness can be assessed reliably using spirometry to assist diagnosis and potentially guide and evaluate therapeutic interventions.

▸ An understanding of within-subject variability and responsiveness in health should be considered when interpreting results.
This study aimed to assess the within-day repeatability and between-occasion reproducibility of spirometric outcomes in preschoolers with physician-diagnosed asthma and healthy controls, and compare response to bronchodilator between these groups.

METHODS

Subjects
Preschool children, aged 3–6 years, with mild to moderate asthma diagnosed by a physician specialised in immunology were recruited from the Outpatient Clinic at the Hospital Dona Estefania, Lisbon (March 2006 to March 2009). Healthy preschoolers who had been born full-term with appropriate birth weight and without any significant prior medical history including lower respiratory illness, wheeze or allergic disorders were recruited from local Health Clinics.

Ethics Committee approval was obtained, and parents of participating children gave informed written consent.

Pulmonary function tests
All measurements were undertaken by the same technician in Lisbon, where equipment was calibrated daily according to the manufacturer’s instructions. At time of assessments, all children had been free of any respiratory symptoms for at least 3 weeks. In asthmatic children, bronchodilators were withheld for at least 48 h.

Weight and height were measured using digital scales and a calibrated stadiometer. Baseline spirometry was assessed using the MasterScreen Body Jaeger spirometer (V.4.65, Jaeger, San Diego, USA) according to recent international guidelines. All PFT values were expressed as z-scores, which adjust for sex, age, and height.

Sample size and statistical analysis
Given the need for families to attend twice within a month, it was anticipated that recruitment of healthy children would be more difficult than those with asthma. Power calculations were therefore based on uneven groups. It was estimated that complete datasets in 40 asthmatics and 20 controls would provide 80% power to detect a difference of 0.8 z-scores between asthmatics and controls at the 5% significance level for the selected outcome variables. When examining within-subject differences (ie, change in lung function following either placebo or salbutamol on the same day, or differences in baseline measurements between two occasions), there would be 80% power to detect a within-subject difference of 0.45 z-scores with 20 subjects in each group. This equates to a change of approximately 6% for forced expired volume in 0.75 s (FEV<sub>0.75</sub>) and 7% for forced vital capacity (FVC) and 18% for forced expiratory flow between 25% and 75% of the FVC (FEF<sub>25-75</sub>). Comparisons of demographic details and lung function between study groups were performed using independent sample t tests (when data were normally distributed) with 95% CI and tests for proportions.

RESULTS

Population characteristics
Consent was obtained for 91% of the eligible index children from the asthma clinic, of whom 86% (43/50) successfully completed the full study protocol (figure 1). At the time of assessments, asthmatic children were clinically stable and receiving regular asthma treatment, with 84% (36/43) receiving inhaled corticosteroids. Of the 90 families of healthy children approached, 38 (42%) consented, of whom 87% had successful baseline spirometry. Of these 58% (22/38) completed the study. Lack of parental consent for bronchodilation (24%) was the major reasons for attrition among the healthy controls (figure 1). Success rates for obtaining technically satisfactory spirometry were similar between the groups, but successful results were associated with increasing age of the child (32/48 (67%) <4 years vs 33/40 (83%) 4–6-year-olds).

The population characteristics for those completing the study protocol are presented in table 1. There were no significant differences between groups with respect to birth characteristics, sex, age or weight at time of test, although asthmatic children were slightly taller than controls. A large proportion of children in both groups were exposed to environmental tobacco smoke, especially in those with asthma. As expected, prevalence of family history of atopy was higher among the asthmatic children.

Comparison of baseline pulmonary function results at first visit
Up to 15 forced expiratory flow-volume manoeuvres were obtained (median range: 5<sup>4–13</sup>) from each child during each of the four measurement sessions from which the best curve was selected. At the first test occasion, baseline measurements of z-FEV<sub>0.75</sub>, z-FEV<sub>1</sub> and z-FEF<sub>25-75</sub> were significantly lower in asthmatic children than the controls (table 2).

Within-occasion repeatability (CR<sub>W</sub>): effect of placebo
There were no significant group changes in any of the lung function outcomes in response to the placebo inhaler in either the controls or those with asthma (figure 2, table 3(a)).
Nevertheless, changes within individuals could be considerable; the mean within-occasion coefficient of repeatability (CRw; ie, twice the SD of within-subject changes) for FEV0.75 being 10.4% in asthmatic and 13.2% in healthy children and considerably higher for FEF25–75 (table 3(a)).

**Bronchodilator responsiveness**

Differences in baseline spirometry between healthy and asthmatic preschoolers were no longer evident post bronchodilator (table 2). After salbutamol was administered to the healthy controls, there were significant improvements (relative change from baseline) in FEV0.75, FEV1 and FEF25–75, whereas FVC was unchanged (table 3(b)). Among those with asthma, all outcomes improved significantly after administration of salbutamol. With the exception of FVC, asthmatic children demonstrated significantly larger bronchial responsiveness compared with controls (table 3(b), figure 2), the most marked difference in BD response between groups being seen for FEV0.75. The interpretation of results remained the same whether using relative change from baseline or change on the z-score scale.

**How much change in response to bronchodilator is clinically significant?**

Based on our sample of 22 healthy controls, the threshold for a positive BDR (ie, mean difference + 2SD following placebo) using spirometry would be an increase of 14% for FEV0.75 or FEV1 or 33% for FEF25–75 to be outside the range of variability observed in response to placebo.

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**Table 1** Background characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Asthma (n=43)</th>
<th>Controls (n=22)</th>
<th>Δ (95% CI) Asthma–controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, weeks</td>
<td>38.7 (1.4)</td>
<td>38.6 (0.9)</td>
<td>0.01 (–0.6 to 0.6)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>28 (65%)</td>
<td>10 (45%)</td>
<td>20% (–6% to 45%)</td>
</tr>
<tr>
<td>Age at first test, years</td>
<td>5.1 (0.8)</td>
<td>5.1 (0.9)</td>
<td>0 (–0.4 to 0.5)</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>34 (79%)</td>
<td>9 (41%)</td>
<td>38% (14% to 62%)**</td>
</tr>
<tr>
<td>(a) Asthma</td>
<td>34 (79%)</td>
<td>0</td>
<td>79% (67% to 91%)</td>
</tr>
<tr>
<td>(b) Eczema</td>
<td>3 (7%)</td>
<td>0</td>
<td>7% (0% to 15%)</td>
</tr>
<tr>
<td>Current ETS exposure</td>
<td>34 (79%)</td>
<td>12 (55%)</td>
<td>25% (1% to 48%)*</td>
</tr>
<tr>
<td>(a) Maternal smoking</td>
<td>17 (40%)</td>
<td>4 (18%)</td>
<td>21% (–3% to 45%)</td>
</tr>
<tr>
<td>(b) Paternal smoking</td>
<td>25 (58%)</td>
<td>11 (50%)</td>
<td>8% (–17% to 34%)</td>
</tr>
</tbody>
</table>

Data shown as mean (SD) for continuous and n (%) for categorical variables. Δ=mean difference between groups; *p=0.05; **p<0.001. ETS, environmental tobacco smoke.
Variability of lung function between occasions (reproducibility)

Repeat measurements were performed 3–23 (median 7) days after the first visit for asthmatic children and 3–13 (median 6) days for the controls. In both groups, mean results for all outcomes were similar on both test occasions. There were no significant changes in any lung function outcome over this period in either group. In contrast to healthy controls in whom variability between occasions (CRb) was very similar to that in either group. In contrast to healthy controls in whom variability were similar on both test occasions. There were no significant changes in any lung function outcome over this period in either group. In contrast to healthy controls in whom variability between occasions (CRb) was very similar to that seen in health (CRb for asthmatic children being 26% and 45% for FEV1.75 and FEF25–75), the CRb for all spirometric outcomes was up to twice as high as the CRw in asthmatic children and approximately double that seen in health (CRw for asthmatic children being 26% and 45% for FEV1.75 and FEF25–75, respectively).

DISCUSSION

This study demonstrates the feasibility of assessing BDR in using spirometry in 3–6-year-olds, with 86% providing technically acceptable baseline measurements, and the majority successfully completing paired measurements. The results also provide important new information for this age group regarding within- and between-test variability of lung function in those with doctor-diagnosed asthma when compared with their healthy peers. Results suggest that a large proportion of healthy

Table 2 Comparison of: (a) baseline and (b) postbronchodilator results in 43 children with asthma and 22 healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Control</th>
<th>Δ (95% CI) Asthma—control</th>
<th>Asthma</th>
<th>Control</th>
<th>Δ (95% CI) Asthma—control</th>
</tr>
</thead>
<tbody>
<tr>
<td>z-FEV1.75</td>
<td>−0.77 (1.1)</td>
<td>0.14 (1.0)</td>
<td>−0.91 (−1.5 to 0.3) **</td>
<td>0.20 (1.0)</td>
<td>0.40 (1.1)</td>
<td>−0.20 (−0.8 to 0.4)</td>
</tr>
<tr>
<td>z-FEV1</td>
<td>−0.49 (0.9)†</td>
<td>0.30 (1.0)†</td>
<td>−0.79 (−1.3 to 0.3) **</td>
<td>0.21 (0.8)</td>
<td>0.43 (0.9)</td>
<td>−0.22 (−0.7 to 0.3)</td>
</tr>
<tr>
<td>z-FVC</td>
<td>−0.02 (1.0)</td>
<td>0.29 (1.0)</td>
<td>−0.31 (−0.8 to 0.2)</td>
<td>0.48 (0.9)</td>
<td>0.32 (1.0)</td>
<td>0.16 (−0.3 to 0.7)</td>
</tr>
<tr>
<td>z-FFEF25–75</td>
<td>−1.20 (1.0)</td>
<td>−0.19 (0.7)</td>
<td>−1.0 (−1.5 to 0.5) ***</td>
<td>−0.26 (0.9)</td>
<td>0.21 (0.7)</td>
<td>−0.46 (−0.9 to 0.0)*</td>
</tr>
</tbody>
</table>

Results are expressed as mean (SD) z-scores which adjust for sex, height and age at time of testing. *Text in italic indicates significant differences between groups; figure 2 shows these results expressed as % change rather than z-scores.

*p<0.05; **p<0.01; ***p<0.001.

†FEV1: n=43 for asthma and 19 for controls due to forced expiratory time being <1 s in the remaining four children.

FEF25–75, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV1, forced expired volume in 1 s; FVC, forced vital capacity.
techniques such as the interrupter or forced oscillation technique that requires less subject cooperation. However, in keeping with other recent results, this study demonstrated that provided a suitable child-friendly environment is available, staff are intensively trained and there is strict adherence to appropriate quality control criteria, a high success rate for acceptable spirometric measurements can be obtained in preschoolers both prebronchodilator and postbronchodilator, with less variability within and between subjects than that observed for lung function tests that require less subject cooperation.

Despite its potential usefulness, assessing bronchial responsiveness can be fraught with problems at any age, including which test or outcome to use, which dose of bronchodilator to administer, what threshold best discriminates between subjects and how best to express results.81 7

Additional strengths of the study included assessing the variability of measurements at intervals relevant to the intended uses of the tests, which included within-occasion repeatability with which to interpret response to BD as well as variability over a matter of days or weeks which could be relevant in clinical management or used as objective outcomes in clinical trials. Of particular importance was the finding that, despite the lack of any significant mean change in any outcome in either group over a period of several weeks, the within-subject variability between test occasions in asthmatic children was double that observed in their healthy counterparts, despite the fact that they were studied during periods of clinical stability and without any change in therapy.

CONCLUSIONS

BDR can be assessed reliably using spirometry in wheezy 3–6-year-olds, provided that the technique is suitable adapted for this age group and both within-subject variability and responsiveness in health are taken into consideration. It is recommended that FEV0.75 is used as a primary outcome when assessing BDR in this age group since it appears to be a more discriminative outcome at this age.

Acknowledgements The authors thank the children and families for participating in the study. Part of the data from this study was reported as an abstract.43

Contributors LMB and JS were responsible for the conception and design of the study. AFH provided supervision and auditing of data collection and analysis. JA, PLP and RP assisted with recruitment of subjects. IA and LMB performed the tests and analysed the lung function data. SS, JS, LM and AFH were responsible for the statistical analysis, data interpretation and drafted the manuscript. All authors read the manuscript and approved its intellectual content.

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Competing interests None.

Patient consent Obtained from the parents.

Ethics approval The Research Ethics Committee for Dona Estefania Hospital, Lisbon, Portugal.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


Table 3 Comparison between asthmatic children and healthy controls with respect to: (a) within-subject, within-occasion repeatability following placebo and (b) response to bronchodilator

<table>
<thead>
<tr>
<th>(a) % Change from baseline after placebo</th>
<th>(b) % Change from baseline after BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma Control 95% CI--control</td>
<td>Asthma Control 95% CI--control</td>
</tr>
<tr>
<td>FEV0.75 2.1 (5.2) 2.1 to 3.9</td>
<td>15.0 (12.0)** 4.5 (5.1)** 10.5 (5.1 to 15.8)**</td>
</tr>
<tr>
<td>FEV1 2.6 (7.5) 2.3 to 4.7</td>
<td>10.7 (9.9)** 4.7 (6.8)** 6.0 (1.1 to 11.0)*</td>
</tr>
<tr>
<td>FVC 1.4 (8.1) 2.6 to 2.9</td>
<td>7.6 (10.2)** 2.5 (6.1) 5.0 (0.3 to 9.8)*</td>
</tr>
<tr>
<td>FEF25–275 5.7 (17.4) 2.3 to 15.8</td>
<td>38.8 (34.8)** 11.7 (18.4)** 27.1 (11.2 to 43.0)**</td>
</tr>
</tbody>
</table>

Significant changes from baseline are shown as *p<0.05, **p<0.01, and ***p<0.001 and are indicated for the response to intervention (placebo or BD) within each group. The 95% CI of the differences indicate the response following placebo or salbutamol between children with asthma and healthy controls. BD, bronchodilator; FEF25–275, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV0.75, forced expired volume in 0.75 s; FEV1, forced expired volume in 1 s; FVC, forced vital capacity.


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