Lung Function Impairment Evidenced by Sequential Specific Airway Resistance in Childhood Persistent Asthma: A Longitudinal Study

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Background. Specific airway resistance (sRaw) is virtually independent of lung growth, height, and gender, thus facilitating longitudinal follow-up. Objective. To assess whether a specific phenotype of asthmatic children with a decline in lung function can be evidenced using sRaw. Methods. The authors hypothesized that sequential sRaw measurements over a long period would detect subtle trends. Clinical and functional data of children with persistent asthma under inhaled corticosteroids, evaluated at least three times per year for at least 4 years, were retrieved from a database. Results. One hundred fourteen children (30 girls) were followed for (median [interquartile range]) 6.9 years [5.6–7.9]. Data from 1699 measurements of sRaw (median 14/child) allowed the calculation of individual slopes of sRaw plotted against time demonstrating stable values in the group as a whole between 4 and 18 years. A positive correlation between individual slopes and the degree of intraindividual variation of sRaw was observed (R² = .16; p < .0001). Children with more than one positive skin test showed larger intrasubject variation of sRaw (p = .011). In 19/114 children (17%), a significant increase in sRaw of 12.3% per year (median) was observed. As compared to children without, those with a significant increase in sRaw were boys (p < .0001), had a lower initial (p = .008) and a higher final resistance (p = .025) but did not differ in terms of inhaled corticosteroid dose.

Conclusion. This retrospective study identifies a specific phenotype of asthmatic children that develops an impairment of lung function, confirming the results of a post hoc analysis of the Childhood Asthma Management Program study.

Keywords airway resistance, asthma, childhood, lung function, remodeling

INTRODUCTION

Cross-sectional studies have consistently shown that lung function in patients with clinical asthma is less than predicted. Besides suboptimal treatment at the time of measurement, this finding may reflect any combination of at least four factors as stated by Ulrik: (1) slower growth of lung-function; (2) lower maximally attained level of lung function; (3) earlier onset of decline in lung function; and (4) accelerated decline in lung function (1). Longitudinal studies in adults suggest that the rate of decline in lung function in patients with asthma is greater than that in the nonasthmatic population (2). The magnitude of the excess loss of lung function differs between those studies, but most of them have reported an excess decline in forced expiratory volume in one second (FEV₁) of 5 ± 25 ml per year, airflow limitation occurring in 14% to 24% of the adult patients (1). Whether this accelerated decline in lung function appears and/or could be detected in treated asthmatic children remains debated (2, 3).

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In the Childhood Asthma Management Program study, children randomly received budesonide, nedocromil, or placebo for 5 years, with the change in postbronchodilator FEV₁ as primary outcome variable (4). The investigators found no reduction in the mean FEV₁ among any of the treatment groups over the first 48 months of the study. Subsequently, Covar and colleagues found that 26% of these subjects had a significant decline in lung function (arbitrarily defined as −1% predicted annual decline in pre–β-agonist and post–β-agonist FEV₁), constituting a specific phenotype (5). As elegantly stated by Martinez (3), “abnormal airway remodeling and persistent dysregulation of airway tone might be the final common pathway for different disease mechanisms, and this might explain the heterogeneity of clinical phenotypic syndromes that go under the common label of asthma.”

In this respect, the result obtained by Covar and colleagues in a post hoc analysis deserves to be confirmed. However, as pointed out by Quanjer and colleagues, there are some limitations of a follow-up only based on the percentage of predicted values of forced expiratory flows (6). Indeed, spirometric reference equations that use only height for predicting pulmonary function may be unsuitable for describing the progression of pulmonary function, especially at pubertal age.
2. Discontinuous analysis of sRaw: The duration of follow-up was divided into four equal periods of at least 1 year. For each of the four periods, we calculated the mean values of age, sRaw, and ICS dose. For the fourth period, we further considered the mean values of forced expiratory flows in order to assess whether airflow limitation could be detected in some children at the end of the follow-up period.

**Lung Function Tests**

All tests were performed under regular asthma treatment using a constant-volume whole-body plethysmograph (Masterscope body, Jaeger, CareFusion). The specific resistance (sRaw) was measured by a single-step procedure from the relationship between simultaneously recorded measurements of changes of respiratory flow and changes of plethysmographic volume (slope between ±0.5 L·s⁻¹; sRaw₀.5), omitting the measurement of thoracic gas volume (7). The mean of at least 10 technically satisfactory specific resistance loops recorded during panting (frequency 100/min ± 20) was collected. This technique facilitates opening of the glottis and limits the overestimation of sRaw measured at low frequency due to BTPS (body temperature, pressure, water vapor saturated) correction (13). Spirometry was performed according to international guidelines. Reference values were based on equations used in Europe (6) edited by Zapletal et al. (14).

**Statistical Analysis**

The data were summarized as frequencies and percentages for categorical variables and as median [interquartile range, IQR] for continuous variables. We plotted individual sRaw values against age. We used individual linear regression models between airway resistance and age. Patients with a regression line slope significantly different from 0 (two-tailed .05 significance level) were considered to have an impairment in lung function. Then, we superimposed the average trends of sRaw over time because subjects were assessed at different time points. It is noteworthy that our subjects were analyzed based on an individual course: significance of their own slope of reduction in lung function. Consequently, if a subgroup with decline of lung function is identified, regression towards the mean cannot be inferred (regression towards the mean is a consequence of post hoc selection of an extreme subgroup).

Differences between the impaired and nonimpaired groups were assessed by the chi-square or Fisher’s exact test for categorical variables and a two-sample Mann-Whitney test for continuous variables. Two-tailed \( p < .05 \) were deemed significant. Analyses were performed using SAS 9.1 software.

**RESULTS**

Data of 114 asthmatic children were retrieved from the database. Demographic and clinical characteristics of the study population are shown in Table 1.

**Continuous Analysis of sRaw Over Time**

A total of 1699 sRaw was analyzed. All individual time courses of sRaw measurements are shown in Figure 1. There was a large intersubject variation in specific airway resistance (sRaw) values, i.e., 45% [34–60]. For the whole study group, the mean value of the slope of sRaw was +5.1% [0.9–9.2]
per year, which is not significantly different from zero, thus reflecting the absence of any significant decline in lung function. We further detected a weak positive correlation between the slope of sequential sRaw values and the degree of intrasubject variation (SD value of all sRaw measurements for one child) of the sRaw during the follow-up ($R^2 = .16; p < .0001$). Furthermore, children with more than one positive skin test showed a larger intrasubject variation of sRaw ($p = .011$) as compared to those without or only with one positive skin test. In contrast, the slope of the sRaw was independent of parental atopy, atopic dermatitis, and early onset of symptoms.

Most interestingly, we found a significant decline in lung function, i.e., a slope different from zero in a subgroup of 19 children (17%, impaired lung function) (see Figure 1 and Table 2).

**Sequential Analysis of sRaw Over Time**

The mean sRaw and the mean dose of ICS for each period in the whole group and in the two subgroups are shown in Table 2. The severe asthma children had lower initial and higher final mean sRaw values, although their treatment and their clinical outcome were not different.

**Discussion**

The main result of our retrospective study is the confirmation of the results obtained by Covar and colleagues (see for instance the Figure 1 in their study) (5). More specifically, using a different functional approach (sRaw versus FEV₁) we were able to detect a mild decline in lung function in a subgroup of asthmatic children (~17%). The latter were boys with a better lung function (lower sRaw) at study entry. The differences being that our subgroup of children with an impairment in lung function was selected statistically (regression line slope significantly different from zero) rather than using a predefined definition (a slope of $−1%$ or less per year of postbronchodilator FEV₁% predicted, based on available literature), and that all our children were treated with ICS for moderate to severe persistent asthma.

Our findings are in agreement with the statement of Ulrik concerning an accelerated decline in lung function in some asthmatic patients (1). Early recognition of this specific phenotype with the objective to assess whether new therapies could prevent airway remodeling needs sensitive methods. The earliest change associated with airflow obstruction in small airways is thought to be a slowing in the terminal portion of the spirogram, even when the initial part of the spirogram is barely affected. Unfortunately, forced expiratory maneuver cannot easily be obtained in preschool children, and its results are further influenced by lung growth (15). In contrast, specific airway resistance can be easily measured in preschool children and is independent of height and gender, thus facilitating improving long-term follow-up of the interpretation of measurements carried out longitudinally in children (7). Furthermore, we recently demonstrated that as opposed to a common belief, sRaw is more closely related to FEF₅₀% than to FEV₁, suggesting that sRaw may detect more distal and perhaps earlier levels of obstruction (8). Our main result is to show that a specific phenotype of asthmatic children showing a decline in lung function despite inhaled steroid treatment can be evidenced during childhood. These children did not have more symptoms, as previously suggested (5). The percentage of children with progressively increasing sRaw (17%) is roughly similar to the proportion of adult patients with asthma with a progressive loss of lung function (14% to 24%). Because adult asthmatic patients with airflow limitation have a longer duration of their disease and that they are predominantly males (16, 17), it may be hypothesized that ongoing remodeling of airways occurs in a subset of asthmatic patients from childhood to adulthood, especially in male gender. This specific phenotype was characterized by a better initial lung function (lower sRaw) accordingly with Covar and colleagues (5), which is surprising. Increased bronchomotor tone (higher variability of sRaw) in these children may have favored remodeling and progressive airflow obstruction despite similar levels of ICS during the whole follow-up (see Table 2), suggesting corticoresistance of the remodeling process and/or nonobservance of antiasthma treatment (5, 18).

One may attribute our results to dysanaptic pubertal lung growth. Because sRaw = airway resistance $\times$ thoracic gas...
volume (TGV), at pubertal age a disproportionate increase in TGV may lead to an increase in sRaw. Indeed, a similar phenomenon is evidenced for expiratory flows versus lung volumes that would erroneously be interpreted as airflow limitation (6, 9). Although we cannot rule out this explanation, we do not think that our results are mainly due to dysanaptic lung growth.

The mild degree of airflow limitation that occurs under regular treatment is almost undetectable during the functional follow-up period. It has to be emphasized that this decline in lung function may be related to increased bronchomotor tone and/or remodeling process. Consequently, alternative methods such as exhaled nitric oxide (NO) measurement should be used, because of their correlation with functional impairment in severe asthma (22), and their potential ability to predict lung function decline in asthma (23).

In conclusion, this retrospective study points out and confirms a specific phenotype of children suffering from persistent asthma that is characterized by a decline in lung function, and which can be detected by repeated sRaw measurements.

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DECLARATION OF INTEREST
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

### Table 2

Comparison of the two phenotypes of asthmatic children according to their stability (nonimpaired) or increase of sRaw (impaired) over the study period.

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Impaired subgroup</th>
<th>Nonimpaired subgroup</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>114</td>
<td>19</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Sex ratio, female/male</td>
<td>30/84</td>
<td>0/19</td>
<td>30/65</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age at first LFT, years</td>
<td>6.3 [4.7–7.9]</td>
<td>5.8 [4.3–6.5]</td>
<td>6.4 [4.8–8.2]</td>
<td>.075</td>
</tr>
<tr>
<td>Slope of the sRaw, % per year</td>
<td>+5.1 [0.9–9.2]</td>
<td>+12.3 [10.7–19.0]</td>
<td>+3.5 [0.4–7.2]</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

#### Period 1

| Mean age, years | 7.1 [5.7–8.8] | 6.4 [5.0–7.3] | 7.2 [5.8–8.9] | .066 |
| Mean sRaw, kPa | 0.82 [0.66–0.98] | 0.77 [0.57–0.82] | 0.86 [0.68–0.99] | .008 |

#### Period 2

| Mean sRaw, kPa | 0.81 [0.70–0.92] | 0.70 [0.65–0.85] | 0.83 [0.72–0.90] | .071 |

#### Period 3

| Mean age, years | 10.5 [9.2–12.4] | 10.5 [8.7–11.3] | 10.5 [9.3–12.6] | .30 |
| Mean sRaw, kPa | 0.87 [0.73–1.01] | 0.85 [0.70–1.01] | 0.87 [0.73–1.01] | .95 |

#### Period 4

| Mean sRaw, kPa | 0.93 [0.81–1.10] | 1.01 [0.96–1.14] | 0.92 [0.80–1.10] | .025 |

### Note

- IQR = interquartile range; LFT = lung function test.
- *p value between children depicting either in increase or a stability of sRaw.
- ICS dose denotes the mean dose per day of inhaled corticosteroid treatment expressed as beclomethasone equivalent as defined by GINA guidelines (12).