Bronchial obstruction and reversibility in children: inspiratory or expiratory resistance?

To the Editor:

Assessing bronchial obstruction and reversibility is of help in diagnosing asthma. The forced oscillation technique (FOT) has gained popularity in children since minimal cooperation is required. Owing to the fact that measurements are performed during tidal breathing, the upper airway may significantly impact on the respiratory resistance \((R_s)\) [1, 2]. The glottic aperture narrows during tidal expiration [3], contributing to \(R_s\) being larger in inspiration [2, 4, 5]. Acute bronchial obstruction promotes further laryngeal narrowing [6–8], which is expected to impact the \(R_s\) measured during expiration. It is not known to what extent the mechanism is present in children with stable asthma, or whether the ability of \(R_s\) to diagnose bronchial obstruction and reversibility is impeded in expiration. With a single excitation frequency, \(R_s\) may be described along the respiratory cycle and computed in expiration \((R_{s,e})\) and inspiration \((R_{s,i})\). The aim of this study was to compare \(R_{s,i}\) and \(R_{s,e}\), their response to salbutamol and respective ability to separate asthmatics from controls. The hypothesis was that the diagnostic value of \(R_{s,e}\) and its response to bronchodilator inhalation is impeded compared with \(R_{s,i}\).

Patients with asthma were diagnosed in the local paediatric pulmonology clinic (Hôpital d’enfants, CHU de Nancy, Nancy, France). All had discontinued their bronchodilator therapy \(\geq 12\) h prior to the study. Age-matched healthy children served as controls. Written informed consent was obtained and the study was approved by the Ethics Committee (Comité de Protection des Personnes EST III, CHU de Nancy, Nancy, France). Pressure was oscillated at 8 Hz around the child’s head to minimise upper airway wall motion (Pulmosfor; SEFAM, Villers-lès-Nancy, France). The measured signals were displayed and quality-controlled at the end of the acquisition, and \(R_{s,i}\) and \(R_{s,e}\) were averaged separately. Subsequently, forced spirometry was performed (Masterscope; Erich Jaeger GmbH, Wuertzburg, Germany). Measurements were repeated 10 min after inhalation of 200 \(\mu\)g salbutamol (Ventoline; GlaxoSmithKline, Marly Le Roi, France). Data were compared using ANOVA and Fisher’s t-test as needed. The ability of \(R_{s,i}\) and \(R_{s,e}\) and the percentage change in these values induced by salbutamol \((\Delta R_{s,i} \text{ and } \Delta R_{s,e})\) to separate asthmatics and controls was tested by calculating, at relevant thresholds, the Youden index, which is the simple sum of sensitivity and specificity minus one. It ranges from -1 for a nondiagnostic test to +1 for the ideal test. Maximal values \((Y_{\text{max}})\), corresponding sensitivity, specificity and threshold are reported.

55 asthmatics (36 males) and 23 controls (10 males) entered the study. 27 were taking inhaled steroids. Age, height and forced expiratory volume in 1 s (FEV1) \(z\)-score [9] were similar between groups (table 1). Asthmatics showed significantly larger \(R_{s,i}\) and \(R_{s,e}\) \((p \leq 0.001)\) compared with controls. \(R_{s,e}\) was larger than \(R_{s,i}\) in both groups \((p < 0.001)\), but the difference between expiration and inspiration tended to be larger in asthmatics than controls \((p = 0.07)\) (table 1) and was negatively correlated with FEV1 \(z\)-score \((r = -0.35, p < 0.01)\). \(Y_{\text{max}}\) was larger for \(R_{s,e}\) than \(R_{s,i}\) \((0.49 \text{ versus } 0.46)\) at respective thresholds of 8.6 hPa·s·L\(^{-1}\) and 7.0 hPa·s·L\(^{-1}\)). The corresponding specificity was larger for \(R_{s,e}\) \((0.87)\) than \(R_{s,i}\) \((0.70)\), but sensitivity was lower \((0.62 \text{ versus } 0.76)\). Asthmatic children presented a larger response to salbutamol than controls by both \(R_{s,i}\) and \(R_{s,e}\) \((p < 0.007)\) (table 1). While the response was larger in inspiration than expiration \((p < 0.0001)\), \(\Delta R_{s,e}\) showed a larger \(Y_{\text{max}}\) than \(\Delta R_{s,i}\) \((0.49 \text{ versus } 0.37)\) at respective thresholds of -15% and -19%, with a corresponding better specificity \((0.75 \text{ versus } 0.65)\) and sensitivity \((0.74 \text{ versus } 0.72)\).

Altogether, the hypothesis that the ability of \(R_s\) to identify asthma would be less in expiration than inspiration was not verified. Larger \(R_{s,e}\) than \(R_{s,i}\) at baseline are in keeping with prior reports from the literature [2, 4, 5]. Lung volume, a major determinant of airway resistance, would be unlikely to play a significant role, provided the time-triggered signal sampling did not bias the computation of tidal volume, due to asymmetry of breathing flow between inspiration and expiration. The fact that the difference between \(R_{s,e}\) and \(R_{s,i}\) obtained with similar digitisation protocols, is not regularly found during artificial ventilation through an endotracheal tube in adults [10] or infants [11] gives indirect support to a role for the upper airways.
Glottis narrowing during expiration [3, 5] increases the upper airway resistance, particularly the nonlinear component [2]. Similar glottis responses in patients and controls would tend to blunt the difference related to the bronchoconstriction. In fact, a trend for a larger difference between expiration and inspiration was observed in asthma versus controls, a difference that related to the degree of airway obstruction. An interpretation of these findings could be that glottis adduction occurred in such a manner that the Rs difference relative to control was reinforced during expiration. In other words, the laryngeal constriction would relate to the airway obstruction in children with stable asthma, as previously reported in adults during acute spontaneous or induced asthma [6–8].

Ymax was larger for Rrs,e than Rrs,i, suggesting the ability of FOT to separate controls from stable asthmatics was enhanced during expiration. Furthermore, the higher specificity of Rrs,e suggests a better identification of patients, i.e. fewer false positive responses, than that of Rrs,i. Threshold values disclosed for Rrs,e and Rrs,i with the current cut-up may not be extrapolated to other FOT variants, since varying pressure around the head has been shown to provide larger Rs than for standard input impedance. In addition, minimising the upper airway artefact was probably helpful in sharpening the Rs difference between expiration and inspiration.

Compared with ΔRrs,i, ΔRrs,e provided better discrimination between patients and controls, improving specificity and sensitivity, suggesting the reflex relaxation of laryngeal adductors associated with the bronchodilatation potentiated the magnitude of the overall response in asthma. Different decision levels have been previously reported for ΔRs [12]. The current 15% decrease with Rs,e is somewhat lower than the -30% Rs cut-off reported by C ALOGERO et al. [13], who used a standard input impedance device and estimated the threshold from the 95% confidence interval of healthy subjects in a large two-centre study, rather than from sensitivity–specificity analysis.

Finally, the potential of measuring Rs,e by varying pressure around the head and its response to 200 μg inhaled salbutamol in this cohort of children with stable asthma may not generalise to other conditions. In about half of the patients, inhaled steroids possibly had an indirect effect as a result of improving baseline obstruction, and a different picture might, thus, be observed in children with more severe bronchoconstriction or in response to a larger salbutamol dosage. In a completely different context, Rs,e, rather than Rrs,e, was recommended in patients with chronic obstructive pulmonary disease, because expiratory flow limitation during tidal breathing is responsible for large Rs swings [14] that result from the increase in airway impedance at the choke point [15].

We conclude that the ability of Rs to separate asthmatic from healthy children is enhanced during expiration compared with inspiration, based on both measurement at baseline and assessment of response to bronchodilator. A likely mechanism relates to more pronounced expiratory glottis adduction in children with stable asthma compared with controls, reinforcing the group difference in Rs,e at baseline and in response to salbutamol. The expiration-related measurement improves specificity and appears to ease the identification of patients while decreasing the rate of false negative responses.

### Table 1: Subject characteristics, baseline lung function and response to salbutamol

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Asthma</th>
<th>p-value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>23</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>7.8 ± 1.8</td>
<td>8.1 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Height cm</td>
<td>130 ± 14</td>
<td>129 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1 z-score</td>
<td>0.6 ± 1.1</td>
<td>0.3 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Rrs,i hPa·s·L⁻¹</td>
<td>6.8 ± 2.0</td>
<td>10.0 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rrs,e hPa·s·L⁻¹</td>
<td>0.6 ± 0.8</td>
<td>1.2 ± 1.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Rrs,e-i hPa·s·L⁻¹</td>
<td>0.6 ± 0.8</td>
<td>1.2 ± 1.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Subjects n</td>
<td>20</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>ΔRrs,i %</td>
<td>-18 ± 11</td>
<td>-28 ± 15</td>
<td>0.006</td>
</tr>
<tr>
<td>ΔRrs,e %</td>
<td>-10 ± 15</td>
<td>-23 ± 16</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise stated. FEV1: forced expiratory volume in 1 s; Rrs,i: respiratory resistance during inspiration; Rrs,e: respiratory resistance during expiration; Rrs,e-i: difference between Rrs,e and Rrs,i; ΔRrs,i: change in respiratory resistance during inspiration after salbutamol; ΔRrs,e: change in respiratory resistance during expiration after salbutamol; NS: nonsignificant. #: control versus asthma; *: p<0.0001 versus inspiration; †: p≤0.002 versus inspiration.
Respiratory resistance assessment of bronchial obstruction: better asthma diagnosis in expiration than in inspiration

Iulia Ioan1, Laurianne Coutier2, Claude Bonabel1,2, Bruno Demoulin2, François Marchal1,2, Cyril Schweitzer1,2 and Silvia Varechova1,2

1Service d’Explorations Fonctionnelles Pédiatriques, Hôpital d’Enfants, CHU de Nancy, Nancy, and 2EA 3450 DevAH – Laboratoire de Physiologie, Faculté de Médecine, Université Lorraine, Vandoeuvre, France.

Correspondence: F. Marchal, Service d’Explorations Fonctionnelles Pédiatriques, Hôpital d’Enfants, Rue du Morvan, 54511 Vandoeuvre, France. E-mail: f.marchal@chu-nancy.fr

Received: Oct 17 2013 | Accepted after revision: Feb 25 2014

Support statement: This work was supported by grant EA 3450 from Ministère de la Santé et de la Recherche Médicale.

Conflict of interest: None declared.

Acknowledgements: The authors thank the children who participated and their families, and the primary school “Ecole de Brabois”, Vandoeuvre, France.

References