Observational study of inhaled corticosteroid treatment for improved expiratory variability index in steroid-naïve asthmatic children

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To the Editor:

The Lancet Asthma Commission calls for objective measurements to support asthma diagnosis, especially for children [1]. The expiratory variability index (EVI) is a novel method of testing lung function that can be measured passively at night with an impedance pneumography (IP) technique using four skin electrodes and a small body-worn recorder. The aim of EVI is to measure variation in flow–volume curve shapes within 15–45% of the expired volume. It has been demonstrated that normal variations in the curve shapes are mainly caused by comparing different sleep cycles [2], which are reduced in the presence of bronchial obstructions [3].

IP is feasible for young children, and EVI values have previously been associated with the severity of wheezing episodes in children aged 1–5 years [4, 5]. In previous studies, up to 94% of recordings were successfully made, and EVI values in young children exhibiting wheezing decreased after inhaled corticosteroids (ICS) were withdrawn [5]. In infants, EVI is associated with lung function and the risk of developing asthma [6]. Our aim was to determine whether ICS treatment improves EVI in children aged 4–7 years with doctor-diagnosed asthma.

This study was conducted in a tertiary care hospital (Skin and Allergy Hospital) and a private clinic (Töölö, Mehiläinen), with children monitored for 6 months after starting ICS treatment. Inclusion criteria were age (4–7 years), doctor-diagnosed asthma and a clinical need to start ICS treatment. Exclusion criteria included the use of ICS in the past 30 days, acute respiratory infection in the previous 14 days, preterm birth, another chronic lung disease, or the use of other active medical equipment. In total, 53 children participated in the study, and 21 were excluded from the analysis due to drop out (n=4) or missing EVI values at any visit (n=17). The feasibility analysis was performed on 49 children who took part during every study visit.

After visit I, every child started ICS treatment. Visit II occurred within 43 days (interquartile range 40–48 days) of visit I and visit III was within 68 days (interquartile range 61–71 days) of visit II. Impulse oscillometry (Jaeger GmbH, Würzburg, Germany) and bronchodilation and/or free running tests and the Childhood Asthma Control Test (C-ACT) were performed during every visit. Exercise-induced bronchoconstriction was defined as having a ⩾40% increase in resistance at 5 Hz after exercise. After each visit, IP registration (Ventica, Revenio Research Ltd., Finland) was performed for 2 nights and average values were used in the analysis**.** The EVI was measured by software (Ventica Analytics v2.1.0) that calculates Pearson's correlations among the tidal breathing flow–volume curves of 15–45% of exhaled volume during sleep. The EVI value is represented by the formula $(\log10(\mathrm{IQR}(r))+2)\times10$, in which IQR($r$) is the interquartile range of the correlations. A low EVI indicates reduced variability in tidal breathing flow–volume curves. Any EVI values below 14 were considered abnormal, and the reference values are based on children aged 1–5 years [4, 5].

The Helsinki University Hospital of Children and Adolescents Ethics Committee approved the study and each participant (including parents) provided written informed consent. The study was registered at ClinicalTrials.gov (NCT03377192).

Shareable abstract (@ERSpublications)
Inhaled corticosteroid treatment improves expiratory variability index in steroid-naïve asthmatic children aged 4–7 years https://bit.ly/3n4vBT3

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SPSS version 22 (IBM Corp, Armonk, NY, USA) was used for statistical analysis, and Friedman two-way analysis and the Wilcoxon signed rank test adopted for analysing continuous parametric data at different time points. For categorical data, the Chi-squared and Fisher exact tests (when counts were <5) were employed. In the correlation analysis, Spearman's correlations were used. The statistical significance was established at $p<0.05$.

The median age of the 32 children in the final analysis was 5.1 years (interquartile range 4.6–5.8 years), including 21 (66%) boys. In total, 19 (59%) had doctor-diagnosed wheezing episodes, 12 (38%) had histories of hospital ward treatment, 20 (63%) had atopic eczema, 23 (72%) were sensitised to aeroallergens, and 24 (75%) had positive Asthma Predictive Index. 13 children had no history of doctor-diagnosed wheezing episodes but long-term asthmatic symptoms, and 11 of them were confirmed to have exercise-induced bronchoconstriction through a free running test.

After their baseline visit, most children, 27 out of 32 (84%), started twice daily use of Flixotide Evohaler (Glaxo Wellcome Production; Évreux, France), which provides 125 µg fluticasone per dose. The remaining five children started twice a day a budesonide dry powder inhalator (Budesonid Easyhaler, Orion Pharma; Espoo, Finland), two at 100 µg and three at 200 µg per dose.

After a second visit, one child was switched from the Flixotide Evohaler to a formoterol and budesonide aerosol (Symbicort 4.5/160 µg 1×2, AstraZeneca AB; Södertelje, Sweden), and one was switched from budesonide to a formoterol and budesonide powder inhaler (Bufomix Easyhaler, Orion Pharma; Espoo, Finland). Montelukast was added for treatment of two children at a dose of 4–5 mg·day^{-1}.

Five (16%) of the children had EVI values <14 at baseline; two (6.3%) had these values at visit II, and one (3.1%) at visit III. After ICS, the median EVI values improved significantly from the baseline visit (median 17.5 (15.2–18.9) *versus* 18.4 (17.3–20.0) *versus* 17.9 (17.1–19.6), p=0.028). Further, significant improvements were observed between visit I and II and between visits I and III. The individual results are presented in figure 1.

During follow-up, one child required emergency evaluation due to wheezing the day after the baseline visit. This child exhibited an abnormal EVI value (10.1) that night. At the baseline visit 12 h before the

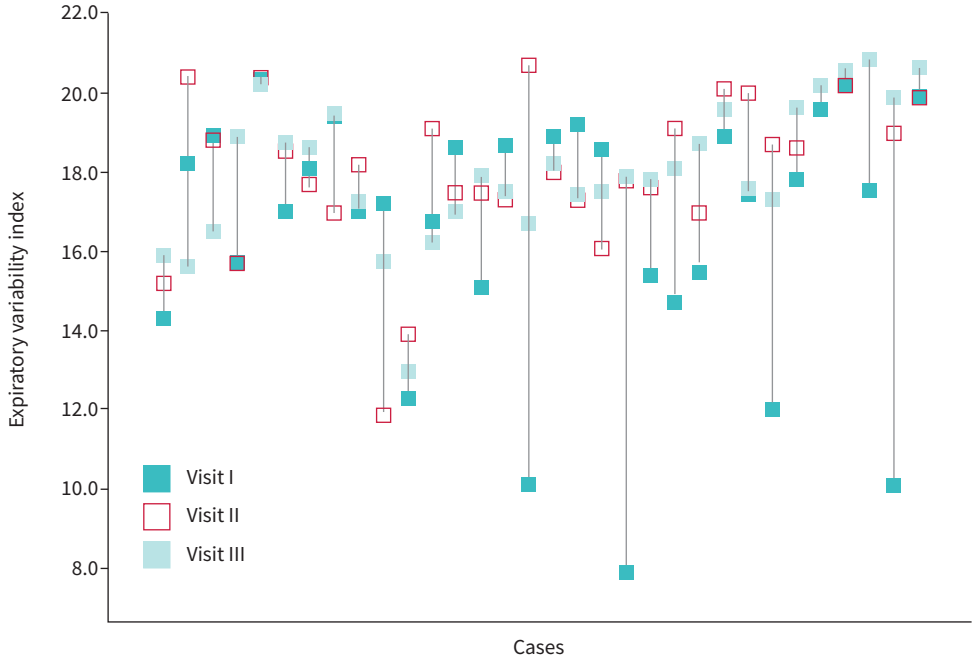

FIGURE 1 Expiratory variability index at every visit for 32 children. In total for 19 out of 32 children the lowest value was observed at visit I before starting inhaled corticosteroid.

emergency visit, lung auscultation was normal, and no obstruction was observed in impulse oscillometry. However, the child experienced significant exercise-induced bronchoconstriction in the free running test and measured 18 points in the C-ACT. At visit II (48 days after baseline) the child exhibited a normal 23 points in the C-ACT, significant bronchoconstriction was not observed in the free running test, and the EVI value improved significantly to 20.7.

Overnight IP registration was successful 220 out of 294 (75%) times. Further, there were no differences between centres, and success was most often achieved at visit II (70/98 (71%) *versus* 84/98 (86%) *versus* 66/98 (67%), p=0.008). The primary reason for failed registrations was a batch of defective electrodes. Minor problems included a lack of registration time (due to short sleeping times) and electrodes that disconnected during sleep. Children who failed both registrations were more often boys (16/17 (94%) *versus* 21/32 (66%), p=0.037) and older children (5.9 (4.8–7.1) *versus* 5.1 (4.6–5.8) years, p=0.045) compared to 32 children who successfully registered at least once every visit.

After ICS treatment, the C-ACT results improved progressively from visit I to visit II and III (median 21 *versus* 23.5 *versus* 24, p<0.001) and acute physician visits due to respiratory symptoms decreased compared with the 6 months before and after ICS began (median (range) 0 (0–3) *versus* 0 (0–1), p=0.017). Further, exercise-induced bronchoconstriction alleviated (median 61% *versus* 16.5% *versus* 13.%, p<0.001), but there were no significant changes in bronchodilatation test (median −21% *versus* −21% *versus* −16%, p=0.12) or baseline lung function defined as resistance at 5 Hz (median 0.06SD *versus* −0.55SD *versus* −0.69SD, p=0.054).

The correlation analysis revealed no significant correlations between EVI values at baseline and oscillometry results at 5 Hz (r_s=−0.038, p=0.835) or reactance at 5 Hz (r_s=0.217, p=0.267). On one hand, no significant correlation was found between EVI and C-ACT score (r_s=−0.085, p=0.645). On the other hand, there were no correlations between C-ACT scores at the baseline visit and impulse oscillometry resistance at 5 Hz (r_s=0.033, p=0.949) or reactance at 5 Hz (r_s=−0.054, p=0.783).

In previous studies, EVI decreased among wheezy hospitalised children aged 1–5 years after ICS ceased and improved significantly immediately after exacerbation during treatment in hospital [4, 5]. In our study of children with relatively mild asthma, concordant with C-ACT scores, significant improvements were observed after starting ICS treatment in older preschool children without recent acute exacerbation. According to our findings, EVI also appears to be associated with asthma control in older children, up to 7 years of age.

Previously, 77–94% of registrations were successful [4, 5, 7]. However, a defective batch of electrodes was the primary reason for the lower rate in our study. Accordingly, 17 out of 49 (35%) were excluded from the final analysis. To ensure successful results, we recommend that registration should be performed for two nights.

No significant correlations were observed between EVI and impulse oscillometry, baseline parameters or C-ACT scores. However, two other studies have found only weak correlations between asthma test scores and both fractional exhaled nitric oxide and forced expiratory volume in the first second of a spirometry test [8, 9].

The strength of our study was that patients were monitored for 6 months. The relatively mild patient population could also be considered a strength, because for those children the diagnosis of asthma is clinically challenging and lung function tests would be required especially for this patient group. A major shortcoming of the study was the significant proportion of excluded children. Moreover, this was an observational study that did not include a healthy control group, and children older than 5 years have no reference values for EVI. In this study, most children already had EVI values >14 at visit I and the proportion of participants with an EVI value below 14 did not differ significantly from that among healthy children aged under 5 years, which is considered normal in children aged 1–5 years. This high proportion of normal test results could be related to a mild disease, or inappropriate reference values for older children.

In conclusion, for children aged 4–7 years with mild asthma, EVI improved significantly after starting ICS. Future studies are needed to explore optimal EVI cut-off values and clinical utility in children in within this age group.

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Conflict of interest: V-P. Seppä holds patents relating to impedance pneumography (IP) and is an employee of Revenio Group, which commercialises IP technology. The other authors declare no conflicts of interest.

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