Received: 5 December 2019 | Revised: 12 February 2020 | Accepted: 13 February 2020

DOI: 10.1111/pai.13234

ORIGINAL ARTICLE

WILEY

Reduced expiratory variability index (EVI) is associated with controller medication withdrawal and symptoms in wheezy children aged 1-5 years

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Funding information
The study was funded unrestricted grants by the Tampere Tuberculosis Foundation, Finnish Funding Agency for Technology and Innovation (Tekes) and Finnish Cultural Foundation. Commercial IP recorders, their accessories and software were provided free of charge by Revenio Research Ltd. for the duration of the study.

Editor: Ömer Kalaycı

Abstract

Background: Lung function testing is an essential part of diagnostic workup and monitoring of asthma, but young children are lacking easy, routine testing methods. However, recent discoveries show reduced tidal breathing variability measured using impedance pneumography (IP) at home during sleep as a sign of airway obstruction. In this study, we assessed (a) the discriminative capacity of expiratory variability index (EVI) between healthy controls and young children with recurrent wheeze on-and-off controller medication, (b) association between EVI and parentally perceived obstructive symptoms (need for bronchodilator) and (c) measurement success rate.

Methods: We included 68 patients (aged 1.0-5.6) and 40 healthy controls (aged 1.0-5.9 years). The patients were prescribed a three-month inhaled corticosteroid (ICS) treatment due to recurrent obstructive bronchitis. We measured EVI using IP at home at the end of the treatment (0W) and 2 (2W) and 4 (4W) weeks after ICS withdrawal.

Results: EVI was higher in controls than in patients, and significant within-patient reduction occurred at 4W as compared to 2W or 0W. Area under curve of the ROC curve (controls vs all patients) at 4W was 0.78 (95% CI 0.70-0.85). Children who were administered bronchodilator by parental decision had lower EVI than those without bronchodilator need at 4W, but not at 0W or 2W. Patients with parent-reported airway infection, but no bronchodilator need, had normal EVI. Measurement success rate was 94%.

Conclusion: EVI was lower in patients than in controls and it reduced further after controller medication withdrawal, especially in the presence of parentally perceived wheeze symptoms. This technique shows a significant potential for routine lung function testing of wheezy young children.

KEYWORDS

asthma, home monitoring, lung function, obstruction, paediatric, tidal breathing, wheeze

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13234

1 | INTRODUCTION

The NHLBI guideline for asthma in the age group of 0-4 years states that asthma is often over- and under-diagnosed leading to inadequate or inappropriate prolonged therapy and that the diagnosis is complicated by the difficulty in obtaining objective measurements of lung function.[1] Lack of routine lung function testing for young children hinders also monitoring of their asthma,[2] and poor disease control is common.[3] Poor asthma control increases the burden of the disease to the society and families through avoidance of physical activities,[4] absence from school,[5] sleep disturbance[3] and more frequent exacerbations[6] resulting in emergency department visits and hospitalisations.

Analysis of tidal breathing flow-volume (TBFV) curves has been studied as an alternative way of assessing lung function in young patients who cannot perform forced exhale manoeuvres. Certain 'static' features of the curves, measured directly from mouth flow, have been associated with the presence of airway obstruction in infants and with increased risk of asthma later in life.[7] Recently, we showed that TBFV indices derived from longer recordings using impedance pneumography (IP) technique during night's sleep are associated with risk of persistent asthma in infants[8] and parentally observed symptoms in wheezy children.[9]

An emerging approach in TBFV analysis is to quantify the level of variability of the curves over time. Reduced variability has been associated with COPD[10] and asthma[11] in adults, and with increased hospitalisation rate[12] and lower airway obstruction and bronchodilator response[13] in infants and children. We showed that the TBFV variability in preschool children is associated with increased risk of persistent asthma.[14] In our earlier study, we also discovered that the obstruction-related pathologic rigidity of the curve is most prominent within a specific section of the curve (15%-45% of exhaled volume).[15]

In this study, we assessed, firstly, the discriminative capacity of a novel tidal breathing parameter (expiratory variability index, EVI) between healthy controls and young children (age 1-5 years) with recurrent wheeze while on controller medication and after its withdrawal; secondly, the association between EVI and parentally perceived obstructive symptoms (need for bronchodilator); and thirdly, the measurement success rate of this IP-based recording system used at home during night's sleep.

Key Message

Recurrent symptoms of lower airway obstruction are common in children aged five and under, but their lung function is not routinely tested due to lack of suitable, easy measurement methods. In this paper we show that a new marker, expiratory variability index (EVI), measured at home during sleep using impedance pneumography provides objective information on lung function of children with recurrent wheeze and may help the clinician in decision making.

2 | METHODS

2.1 | Study subjects

We enrolled 70 patients between September 2014 and March 2017 who visited the emergency room of the Tampere University Hospital (TAUH), Finland, due to recurrent obstructive bronchitis. The patients were eligible if they had had at least three lower airway obstructions diagnosed by a physician in the previous year, ICU-treated exacerbation or one or more pneumonias with wheeze and having at least two obstructive episodes outside pneumonias, and were started on a three-month inhaled corticosteroid (ICS) treatment period as per the Finnish guideline.[16] Children with laryngeal disease, tracheobronchial malacia, parenchymal lung disease or history of bronchopulmonary dysplasia were excluded.

We enrolled 41 healthy control subjects aged 1-5 years through newspaper and social media advertisements in the Pirkanmaa region, Finland, between December 2018 and June 2019. The exclusion criteria were the following: preterm birth; recurrent bronchitis or recurrent hospitalisations because of a respiratory illness; nasal congestion; adenotonsillar hypertrophy; signs and symptoms of sleep apnoea or sleep-disordered breathing; acute respiratory infection or hospitalisation because of an acute illness within 4 weeks prior to inclusion; personal or family history of asthma; recurrent wheezing without respiratory infection, allergic rhinitis, chronic rhinosinusitis or other chronic respiratory disorders; atopic dermatitis; or diagnosed allergic sensitisation.

The ethics committee of the Tampere University Hospital special responsibility area approved the study, and the research was conducted according to the principles of the Declaration of Helsinki. All families gave a written informed consent prior to participation.

2.2 | Study design and methods

Sample size of this study is based on a sample size calculation.

For the controls, we did a physical examination on the day of the inclusion (1st IP measurement) and for the patients a skin prick test (SPT).

The atopic status of the patients was assessed with SPT or measurement of allergen-specific IgE from serum when SPT was not available (2 patients). SPT responses were considered positive if at least one allergen caused a wheal greater than or equal to 3 mm and at least half of the wheal size of histamine. Patients with sensitisation to any of the assessed allergens (egg, cat, dog, birch, timothy) were labelled as atopic and all others as non-atopic.

Patients were followed up for 6 months after the last IP measurement by a paediatric allergologist (MP) to determine their current asthma status. They were labelled as having current asthma if they had been prescribed regular asthma controller medication due

to wheezing evidenced by a physician or reported difficult nocturnal cough or exercise-induced cough or shortness of breath relieved by bronchodilator medication. Patients who did not fulfil the previous criteria but had been prescribed intermittent controller medication due to asthma symptoms were labelled as having possible current asthma. All other patients were labelled as not having current asthma. Asthma risk was stratified as positive or negative using the modified Asthma Predictive Index (mAPI).[17] Only the time after the treatment period was taken into account in this classification.

Parents filled in a diary during each IP measurement day and night to document administered drugs, and symptoms, especially wheeze and cough.

The controls did three home IP recordings on consecutive nights, whereas the patients did the measurements during the last week before ending the ICS treatment period (0W) and at approximately 2 (2W) and 4 (4W) weeks after ICS withdrawal.

2.3 | Tidal breathing analysis

Nocturnal tidal breathing signal was collected using wearable IP recorders (Figure 1). The system comprises four skin electrodes, a portable recorder device in a shirt pocket and an analysis software run on a computer after the recording. IP technique measures changes in the electrical conductivity of the thorax which are linearly proportional to changes in lung volume (ie breathing). By differentiating the (lung volume-oriented) IP signal over time, also relative flow rate signal is obtained. IP does not output absolute values for volume or flow, but the linearity of the curves has been validated to have high agreement with simultaneously measured direct mouth flow during a methacholine challenge test in infants[18] and preschool children.[19]

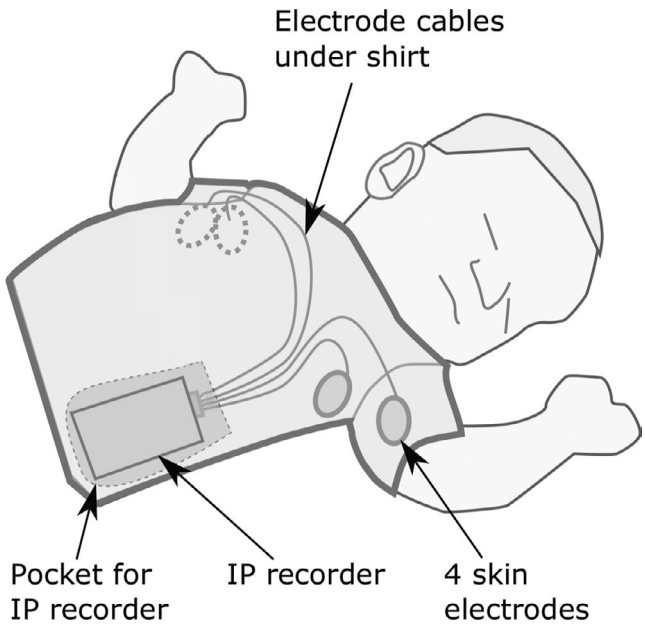

FIGURE 1 Sketch of the impedance pneumography (IP) measurement set-up

Only linearity of the curves, not absolute values, is required for deriving the EVI.

For the patients, university-developed prototype IP recorders were used and for the controls commercial IP recorders (Ventica Recorder, Revenio Research Ltd.). The recorders underwent rigorous comparisons in a test laboratory to confirm that they produce completely interchangeable impedance signals. All recordings were analysed using commercial software (Ventica Analytics 2.1.0) to produce EVI values.

EVI is derived by calculating Pearson's correlations between all partial (15%-45% of exhaled volume), averaged (5-minute window) TBFV curves recorded from the duration of the night's sleep resulting in a large number of correlation values (several thousands). The result is given as $EVI = [\log10[IQR(r)] + 2] \times 10$, where $IQR(r)$ is the inter-quartile range of the correlations. Thus, low EVI value indicates reduced variability of the curves. Curve part of 15%-45% of exhaled volume is used as this has been found most sensitive to discriminate between healthy and obstructive subjects.[15] Sections of recordings containing distortions due to movement, crying, etc, are automatically rejected from the analysis by the software. If there are less than 5 hours of acceptable data, the software does not give an EVI result.

2.4 | Statistical analysis

The analysis was performed using Stata 16 software (StataCorp). Results are given as median with inter-quartile range (IQR), unless otherwise stated.

EVI values from all three measurements of the controls are pooled together for analyses, except when within-subject variability between repeated measurements is analysed.

Statistical tests of two group differences were done with Mann-Whitney *U* test and for three or more groups using the Kruskal-Wallis test. Within-patient changes were tested using the Wilcoxon signed-rank test. Correlations were calculated using Pearson's correlation. Comparison of proportions of dichotomous variables was done using two-sample proportion test with *z*-statistics (prtest). No adjustments for multiple comparisons were made. Test results with *P* values below .05 were considered significant.

3 | RESULTS

3.1 | Characteristics of the participants

Of the enrolled 70 patients, 68 patients entered the study. Two patients were withdrawn before the first IP measurement because of clinical deterioration needing to continue or restart ICS treatment. Two patients did not attempt the third IP measurement due to neglect or need to start ICS. We enrolled 41 control subjects, of which one withdrew their consent.

There was a mismatch in the age between the patients and controls ($P = .0001$) (Table 1).

TABLE 1 Subject characteristics and impedance pneumography measurement success rates

	Patients (N = 68)	Controls (N = 40)
Subject characteristics		
Age at enrolment—years median (IQR, range)	2.4 (1.3, 1.0-5.6)	3.7 (2.2, 1.0-5.9)
Male sex—no. (%)	46 (67)	18 (55)
Inclusion reason—no. (%)		
ICU-treated exacerbation	2 (3)	-
4 or more exacerbations during last year	40 (58)	-
3 exacerbations during last year	11 (16)	-
3 exacerbations during last year w/o asthma risk factors	10 (15)	-
2 exacerbations and pneumonia with wheezing	6 (9)	-
Atopic—no. (%)	29 (42)	0 (0)
mAPI positive—no. (%)	23 (34)	0 (0)
Current asthma at 6-month follow-up—no. (%)		
Yes	37 (54)	-
Possible	16 (23)	-
No	16 (23)	-
Measurement success rates		
All attempts—no.	202	119
Successful—no. (%)	185 (92)	115 (97)
Duration of accepted data per night—hours median (IQR)	7.4 (1.2)	7.5 (1.1)
Failure reasons—no. (%) *		
Electrode contact problems	5 (2)	3 (3)
Short sleep and/or excess movement during night	1 (0)	0 (0)
Device turned off accidentally, battery exhaustion, device malfunction	11 (5)	0 (0)
Child removes the electrodes	0 (0)	1 (1)

58% of the patients had had four or more wheezing episodes in the past 12 months, 31% only three and 9% only two with one or more pneumonias with wheeze in addition. Two patients were included due to ICU-treated exacerbation.

During 28 of the 185 patient measurements (15%), parents reported signs of airway infection. During 12 of these, also obstructive breathing and bronchodilator use were reported.

3.2 | Practical feasibility

Overall success rate of the IP measurement attempts done at home by the parents was 97% for the control subjects and 92% for the patients (Table 1). The university-developed prototype IP recorder, used only for the patients, had some recorder-oriented failures, whereas the commercial recorder did not.

The recordings took place 8.0 (8.0) days before and 10.0 (3.0) and 25.0 (4.0) days after ICS withdrawal for 0W, 2W and 4W time points, respectively.

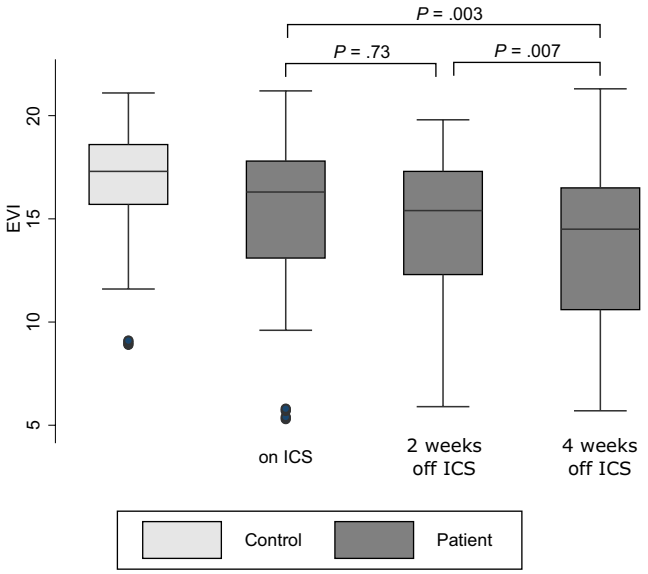

FIGURE 2 Measured expiratory variability index (EVI) values in controls and patients at different time points. *P* values shown only for within-patient changes. The rectangle covers 25th-75th percentile range and the whiskers extend to extremes, excluding outliers, defined as being farther than 1.5 times IQR from the closer quartile. The line in the middle denotes median

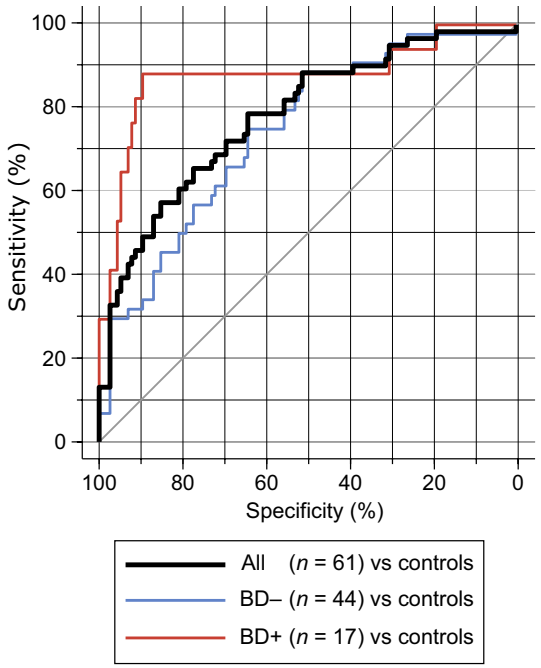

FIGURE 3 Discriminative capacity of expiratory variability index (EVI) presented by ROC curve between controls (115 measurements) and all patients and patients with (BD+) or without (BD−) bronchodilator use at 4W time point [Colour figure can be viewed at wileyonlinelibrary.com]

3.3 | Expiratory variability index

EVI showed weak correlation with age (r = .28, P = .005) in the controls (8% of the EVI variation due is accounted to age). Coefficient of variation of three consecutive measurement nights was 6.6% (4.0).

EVI was higher in controls than in patients (P < .01 for all three time points) (Figure 2). Significant within-patient reduction was observed at 4W as compared to 2W or 0W, but not between 0W and 2W. Area under curve (AUC) of the ROC curve for controls vs all patients at 4W was 0.78 (95% CI 0.70-0.85) (Figure 3). At 4W, children with bronchodilator (BD) use during the same day or night (BD+) (n = 17) showed significantly lower EVI values than those without BD use (BD−) (P = .02) having AUCs of 0.88 (95% CI 0.75-0.99) and 0.74 (0.65-0.82), respectively. Such effect was not significant at 0W (P = .38, n[BD+] = 4) and borderline significant at 2W (P = .07, n[BD+] = 12).

EVI below the 10th percentile of the controls (EVI = 14.0) discriminated between controls and patients at 4W with sensitivity and specificity of 46% and 90%, respectively. At 4W, EVI was below 14.0 in 82% of patients requiring BD and only in 32% of those not requiring BD (Figure 4A). The positive and negative likelihood ratios of EVI below 14.0 to discriminate controls from BD users at 4W were 7.9 and 0.20, respectively, with diagnostic odds ratio of 39.5.

Normal range of within-subject night-to-night variability of EVI in the control subjects as defined by the 5th and 95th percentiles of the changes was −3.3...+3.3 (Figure 4B). Abnormal reduction in EVI (more than 3.3) from 0W to 2W was seen in 13% and from 0W to 4W in 29% of the patients. Abnormal reduction from 0W to 4W was more frequent in patients who used BD (63% of BD+) than those who did not (15% of BD−) (P = .001).

Airway infection without neither shortness of breath nor BD use was parentally reported during 17 measurements (total of all time points). In those occasions, EVI was at the level of the controls (17.3 [5.7], P = .943) and higher than in measurements where no symptoms of any kind were reported (15.8 [4.7], n = 121) (P = .035).

EVI was not different in patients between positive and negative mAPI or between atopic status groups at any time point, but, at 0W, grouping by current asthma showed significant difference between the yes, no and possible categories (P = .009) with EVI values, respectively, as 16.9 (5.2) (n = 32), 16.8 (1.9) (n = 16) and 12.6 (6.5) (n = 13). The difference was not significant at 2W or 4W anymore. Only when excluding the 28 measurements that were conducted during reported airway infection and pooling data from all time points, proportion of mAPI-positive children was significantly higher (P = .03) in those with low EVI (below 14.0) being 44% (24/54) as opposed to 27% (24/89) in children with normal EVI (above 14.0).

EVI was different between the four seasons at 4W (P = .005), but not at 0W or 2W (P = .14 and P = .35, respectively). At 4W, EVI was the highest in the summer (16.4 [2.7], n = 17, June through August) and the lowest in the autumn (10.7 [3.5], n = 9, September through November).

4 | DISCUSSION

This study assesses, for the first time, a recently developed new tidal breathing analysis index, EVI, in children with recurrent wheeze.

Studies of tidal breathing variability have been methodologically diverse, but a general finding has been that airway obstruction is associated with reduced variability as shown in adults with asthma[11] and COPD,[10] children with asthma[13,14] and infants with bronchopulmonary dysplasia.[12] The current association between airway obstruction and tidal breathing variability is mostly empirical, and the specific (neuro)physiological mechanisms linking these two still await further research. During tidal breathing, breaths fluctuate within certain limits, continuously adapting to the changing environment and body's metabolic demand while minimising energy expenditure. The current view is that obstruction reduces the degrees of freedom of the respiratory system, and therefore, breath cycles become more similar to each other.[21] Recently, we showed that changes in sleep stages are a major contributor to TBFV curve shape changes in healthy subjects.[22]

Discriminative capacity of other lung function tests has been studied in case-control settings on older wheezy children without controller medication, similar to our setting at the 4W time point. Bronchodilator response assessed using spirometry has yielded AUC values 0.62-0.71,[23-26] impulse oscillometry 0.66-0.76[27,28] and interrupter technique 0.67[29] (with some patients on controller medication). In this study, we received AUC of 0.78. Importantly, unlike the other tests, IP recording is feasible even in very young children because it requires practically no patient co-operation. However, studies with distinct clinical samples must be compared with caution; the results strongly depend on the pre-test probability for airway obstruction in the patients and the controls. Due to the heterogeneous clinical and physiological characteristics of childhood wheeze, the patients are likely to have considerable variation in the pre-test probability for wheeze within and between studies. Moreover, childhood wheeze is characterised by high variability in symptoms over time. In this study, we allowed the patients to be symptomatic at the time of the testing which is likely to improve the sensitivity of any lung function test, as seen also in our results in a subgroup with bronchodilator use, but some of the studies excluded currently symptomatic patients. Another important matter hindering the assessment of lung function tests is the lack of a definite, reliable reference test for asthma or recurrent wheeze for young children, rendering the diagnosis to a clinical one. On the other hand, our patients were followed up for a longer time period before and after inclusion into the study.

According to our findings, EVI is not associated with recurrent wheeze per se, but more with parentally perceived obstructive symptoms and need for bronchodilator at the time of the measurement (indirectly suggesting the presence of lower airway obstruction). However, this pattern is evident only at time point 4W, not before. This may be

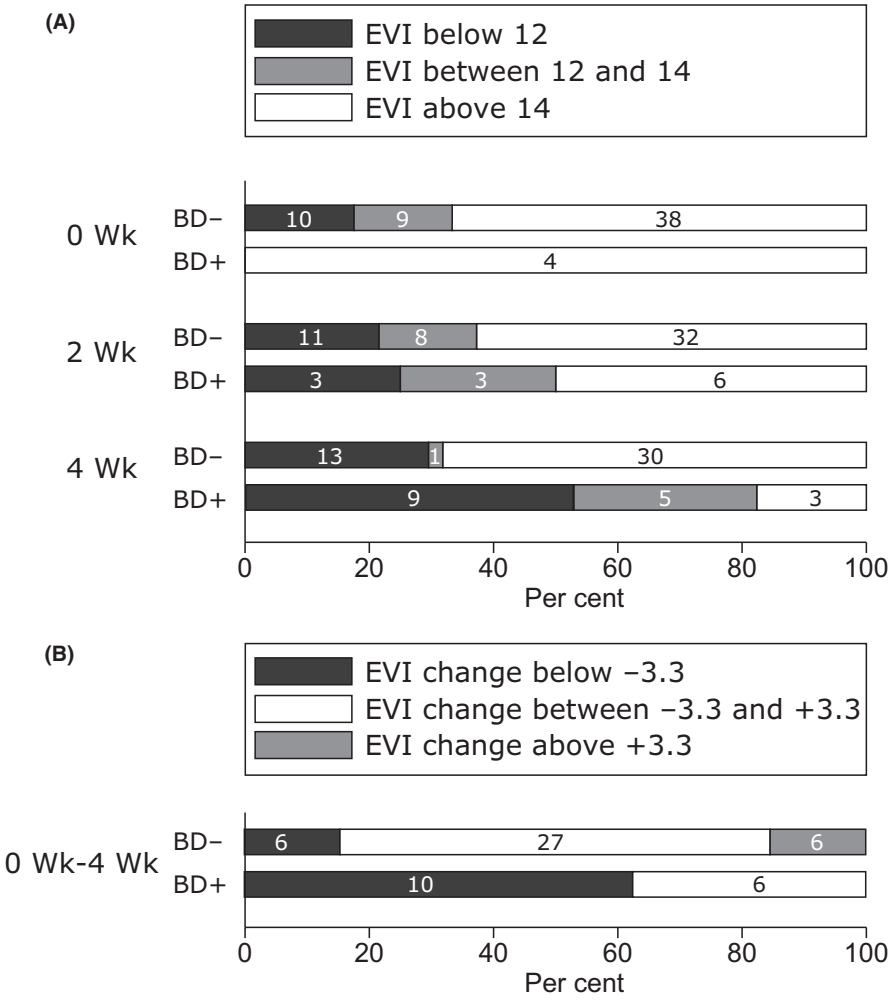

FIGURE 4 Expiratory variability index (EVI) values with respect to limits of normal, study time points (0W, 2W, 4W) and bronchodilator (BD) use. BD+ and BD− indicate bronchodilator was or was not used, respectively, during the EVI measurement day or night. Numbers within the bars refer to the number of patients in each category. Panel A shows the EVI values presented with respect to the 5th and 10th percentiles of the EVI values of the controls (12.0 and 14.0, respectively). Panel B shows the EVI change from 0W to 4W presented with respect to the 5th and 95th percentiles of the changes in the controls (−3.3 and +3.3, respectively)

due to the presumable obstructions being milder at 2W due to still having some effect of ICS. Use of bronchodilator was strongly associated with lower (pathological) EVI result at 4W, which may seem controversial at first, but is likely due to short (approximately 4-6 hours) and incomplete bronchodilation effect of salbutamol. According to the diaries, none of the patients were given bronchodilators after going to sleep. Of interest is also the group with lowered EVI, but no bronchodilator use (present at all time points), that may suggest EVI detected obstruction that was not noticed by the parents.

Analysing the within-patient change in EVI from 0W to 4W as opposed to absolute level of EVI did not significantly improve its discriminative performance. This suggests notable night-to-night variation when EVI is normal, which may be attributed to differences in sleep architecture between nights.[22]

Stratified by current asthma status, EVI was significantly lower in the Possible group at 0 W than in the other two groups. This could be explained by effectiveness of the ICS treatment in the Yes group and no or milder disease in the No group. For the Possible group, ICS treatment may have been ineffective, perhaps due to different disease endotypes not responsive to ICS monotherapy, resulting in lower EVI at 0W.

We also noted a seasonal effect on EVI, it being lowest in the Autumn when respiratory infection incidence is the highest in Finland.[30] This is sensible as infections are a common trigger for obstructions in this age group.

This study is limited by age mismatch between patients and controls and the absence of more established lung function test for confirming the presence of airway obstruction. Validated questionnaire was not used in the parental assessment of airway obstruction, but the findings correlated with the use of bronchodilator. The parents of these children had witnessed several obstructive episodes in their child and likely had more accurate perception of obstruction than persons without such experience. Moreover, all patients had had at least one physician-confirmed obstruction.

This new lung function test has several desirable properties. The measurement can be performed at home by the patient's family and the output is a single, easy-to-interpret number, EVI, which, according to this study, may be insensitive to isolated respiratory infection alone when presented without parentally perceived obstructive symptoms.

We found EVI to be lower in children with recurrent wheeze than in healthy controls. EVI reduced after ICS withdrawal and was lower in children with parentally perceived obstructive symptoms. The IP technique is feasible for routine use, and EVI may provide the clinician with objective, valuable information to support clinical decision-making in young children with recurrent wheeze.

ACKNOWLEDGMENTS

We acknowledge Professor Davor Plavec from Children's Hospital Srebrnjak, Croatia for valuable comments for the manuscript and biostatistician M.Sc. Mika Helminen from Tampere University Hospital, Finland for statistic advice and review.

CONFLICT OF INTEREST

VPS and JV hold patents relating to impedance pneumography. VPS and AH are employees of Revenio Group Corporation that commercialises impedance pneumography technology. JK reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Orion Pharma and Teva outside the submitted work. MP, JK and JGT have no conflict of interest to disclose.

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How to cite this article: Seppä V-P, Paassilta M, Kivistö J, et al. Reduced expiratory variability index (EVI) is associated with controller medication withdrawal and symptoms in wheezy children aged 1-5 years. *Pediatr Allergy Immunol*. 2020;31:489–495. https://doi.org/10.1111/pai.13234