

Exhaled breath temperature as a tool for monitoring asthma control after an attack in children

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Abstract

Background: Exhaled breath temperature (EBT) has been suggested as a non-invasive marker of airway inflammation in asthma. There have been no studies examining longitudinal changes in EBT following asthma attacks.

Objective: To investigate changes in EBT during and after an asthma attack and to relate these changes to changes in respiratory physiological measurements.

Methods: We evaluated 38 hospitalized children aged 5-18 years diagnosed with an asthma attack. Spirometry was performed upon hospitalization. During hospitalization, EBT, peak expiratory flow rate (PEFR), and asthma score were measured daily. These tests were repeated 1 week and 1 month after discharge. The overall PEFR change, temporal changes in plateau values at the end of expiration, and time-dynamic associations were evaluated using linear mixed models.

Results: FEV₁ was lower at admission than at discharge (63.3 ± 24 vs 99.5 ± 14 percent of predicted, $P < 0.001$). The EBT was higher at admission than at 1 week after discharge (34.1°C [range: 33.9 - 34.8°C] vs 33.6°C [range: 33.0 - 34.2°C], $P = 0.007$); overall, EBTs decreased over time ($P = 0.007$). Among individual subjects, decreased EBT was correlated with increased PEFR over time. Furthermore, plateau values at the end of expiration had a time-dependent, dynamic association with the PEFR during hospitalization ($P = 0.005$) and between asthma attack onset and asthma status stabilization ($P = 0.032$).

Conclusions: The EBT was elevated during asthma attacks and gradually decreased until asthma was well controlled. The EBT may be a useful, non-invasive tool for monitoring asthma control in children.

KEYWORDS

asthma attack, children, exhaled breath temperature, peak expiratory flow rate

1 | INTRODUCTION

Asthma is a chronic airway inflammatory disease.¹ Assessing airway inflammation is important for studying the underlying mechanisms of asthma. Although airway inflammation cannot currently be directly measured, non-invasive monitoring for airway inflammation may assist in

the early recognition of asthma, assessment of its severity, and patients' response to treatment, especially during disease exacerbations.^{2,3} Exhaled markers of airway inflammation have become important in the management of childhood asthma; non-invasive markers such as exhaled nitric oxide, albumin, C-reactive protein, and cytokines in exhaled breath condensate have been extensively studied.^{4,5}

Inflammation is a protective response characterized by several classic signs, one of which is heat. Inflammation of the bronchial mucosa increases local vascularization, consequently increasing the bronchial temperature. An increase in measured exhaled breath temperature (EBT) has been hypothesized to reflect the extra heat that is produced from the underlying airway inflammation in asthma.⁶ Therefore, EBT measurements have been suggested as a non-invasive method of detecting and monitoring airway inflammation.⁷⁻⁹ However, no investigations monitoring the longitudinal changes in EBT that occur relative to the asthma status have been performed to date.

The aim of this study was to investigate the longitudinal changes in EBT that occur during and after an asthma attack and to relate these EBT changes to changes in respiratory physiological measurements. Further, we sought to assess the efficacy of using the EBT to monitor asthma control in children.

2 | METHODS

2.1 | Study design

Physicians diagnosed asthma and airway hyperresponsiveness according to the guidelines of the American Thoracic Society, which refer to the presence of episodic respiratory symptoms such as recurrent cough, dyspnea, shortness of breath, and chest tightness, among others.¹⁰ An asthma attack was defined as a worsening of asthma requiring either the use of systemic corticosteroids or hospitalization to prevent a serious outcome; stable asthma was defined as 1) having no asthma exacerbations during the preceding 4 weeks that necessitated systemic corticosteroids or an increased use of inhaled corticosteroids; 2) the use of rescue treatment ≤ 3 times per week; and 3) no clinical indication for a change in medication.¹¹⁻¹³

Children diagnosed with an asthma attack were prospectively evaluated and followed-up for at least 1 month after discharge according to the study protocol presented in Figure 1.

The initial severity of the asthma attack was measured using both a calculated percentage of the predicted peak expiratory flow rate

(PEFR) and an "asthma scoring system" that accounted for the severity of an episode based on signs and symptoms, including the respiratory rate, oxygen saturation, intercostal retractions, and dyspnea.¹⁴ Both assessments were performed daily during hospitalization. Patients performed spirometry immediately after diagnosis. Their bronchodilator (BD) response, fractional exhaled nitric oxide (FeNO) level, and EBT were assessed. Total immunoglobulin E (IgE) and specific IgE levels were measured using the Pharmacia CAP assay (Uppsala, Sweden). Atopy was defined as a specific IgE level ≥ 0.7 KUa/L against more than one allergen or a total IgE level of 150 IU/mL. Respiratory samples collected by nasopharyngeal aspiration were examined using a multiplex polymerase chain reaction panel to identify viral respiratory infections.¹⁵ Sputum samples were obtained to evaluate eosinophilic airway inflammation. Sputum was induced within 24 h after admission; sputum obtained after 24 h because of insufficient post-BD forced expiratory volume in 1 s (FEV₁) was excluded. In addition to obtaining the PEFR, asthma score, and EBT during hospitalization, these items were also assessed during follow-up visits at 1 week and 1 month after hospital discharge. One week following discharge, spirometry with FeNO assessment was repeated. A methacholine challenge test was performed and the FeNO level was measured at the 1-month follow-up visit. In terms of medication used to treat asthma exacerbation, a systemic corticosteroid was administered intravenously during hospitalization and oral prednisolone (for 3 days only) was prescribed after discharge.

This study was approved by the Institutional Review Board of Severance Hospital (protocol no. 4-2014-0460). Written informed consent was obtained from the children and their parents.

2.2 | Study population

We enrolled 50 children with asthma (5-18 years of age) who suffered an asthma attack between May 2014 and September 2016. We excluded four children with a PEFR $\geq 70\%$ or an asthma score < 7 , as they did not meet the criteria for having experienced an asthma attack. Additionally, three patients who were unable to undergo pulmonary

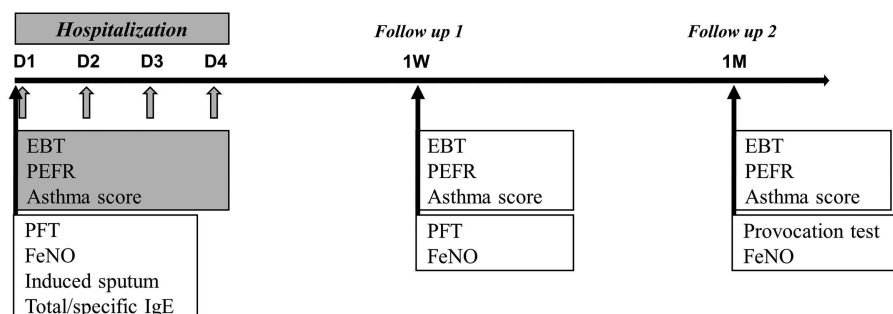


FIGURE 1 Study design. Measurements of the exhaled breath temperature, peak expiratory flow rate, and asthma scores were performed daily during hospitalization and at 1 week and 1 month following discharge. Pulmonary function testing (PFT), fractional exhaled nitric oxide (FeNO) measurements, induced sputum analyses, and allergy tests were performed immediately after admission. We also performed PFT and FeNO assessment at the 1-week follow-up visit. The methacholine challenge test and FeNO measurement were performed 1 month after discharge. D1, day 1 of hospitalization; 1W, 1 week after hospital discharge; 1M, 1 month after hospital discharge

function testing within 24 h and two patients in whom the EBT could not be measured properly due to the severity of their asthma attacks were excluded. One child withdrew consent and three children were re-admitted during the study period after their initial discharge; these individuals were also excluded. Therefore, we ultimately included 38 children in this study.

2.3 | Spirometry and methacholine challenge test

Spirometry (VIASYS Healthcare, Inc., Conshohocken, PA) was performed, and flow-volume curves were obtained according to the American Thoracic Society guidelines before and after BD inhalation.¹⁶ Bronchial hyperresponsiveness was assessed using the methacholine challenge test according to standardized procedures.¹⁷ Each child inhaled increasing concentrations of methacholine (0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5, 10, 25, and 50 mg/mL) nebulized by a dosimeter (MB3; Mefar, Brescia, Italy) until a 20% decrease in the FEV₁ from a post-nebulized saline solution value was achieved. The concentration of methacholine that caused a 20% decrease in the FEV₁ (PC₂₀) was determined, and the challenge was considered positive if the PC₂₀ was ≤ 16 mg/mL.

2.4 | EBT measurements

The EBT was measured using a portable device (X-halo breath thermometer; Delmedica Investments, Singapore), which has been validated in previous studies.^{2,18} Patients were seated and instructed to breathe tidally, inhaling freely through the nose and exhaling into the device.¹⁹ Tidal breathing was maintained until the central heat sink reached a temperature plateau.^{19,20} Each exhalation increased the temperature inside the reservoir chamber until temperature equilibrium was reached.⁶ The plateau value at the end of the expiration (PLET) was recorded.²¹ The EBT was measured each morning during hospitalization after a minimum of 2 h of fasting.

The environmental temperature was controlled^{22,23} at $24.4 \pm 1.8^\circ\text{C}$ and a relative humidity of $47.0 \pm 14.4\%$.

2.5 | Measurements of FeNO

Nitric oxide was measured before pulmonary function tests using a CLD 88 NO analyzer (Eco Medics, Duernten, Switzerland) at a constant expiratory flow rate of 50 mL/s according to American Thoracic Society guidelines.¹⁰ All subjects were asked to avoid food intake and physical exercise for at least 2 h before testing.

2.6 | Sputum induction and processing

Sputum induction and processing were performed as previously described by Yoshikawa et al.²⁴ All children were instructed to wash their mouths thoroughly with water, after which they inhaled a 3% saline solution nebulized in an ultrasonic nebulizer (NE-U12; Omron Co., Tokyo, Japan) at maximum output at room temperature. The children were encouraged to cough deeply at 3-min intervals

thereafter. After sputum induction, spirometry was repeated. If the FEV₁ was $\leq 80\%$ of the post-BD baseline value, the child was required to wait until it returned to the baseline value.²⁵ Sputum samples were kept at 4°C for no more than 2 h before further processing. A portion of the samples was diluted with a phosphate-buffered saline solution containing 10 mmol/L of dithiothreitol (WAKO Pure Chemical Industries Ltd., Osaka, Japan) for cell counting and gently vortexed at room temperature for 20 min. After centrifugation at 400g for 10 min, the cell pellet was resuspended in phosphate-buffered saline. We used trypan blue exclusion to ensure adequate viability. Total cell counts were performed using a hemocytometer, and slides were prepared with cytopsin (Cytospin3; Shandon, Tokyo, Japan) and stained with May-Grünwald-Giemsa stain for differential cell counts. Airway eosinophilia was defined as an eosinophil count $\geq 3\%$ of the total cell count.^{26,27}

2.7 | Statistical analyses

The Wilcoxon matched-pairs test was used to analyze changes in the spirometry parameters between admission and 1 week after discharge for each subject. Correlations between the PLET and some spirometry parameters were determined using the nonparametric Spearman's rank correlation coefficient. Linear mixed models were applied to assess the overall change in the PEF and PLET with time. To determine the relationship between the PLET and other measures over time, the dynamic relationships between the PLET and time-dependent covariates (PEFR, asthma score, and FeNO) were investigated using a random intercept model, including a decomposition of each time-dependent covariate into "within" and "between" components.²⁸ Statistical analyses were performed using the SPSS software (version 22; IBM Corp., Armonk, NY), R (version 3.2.2; The R Foundation for Statistical Computing, Vienna, Austria), and SAS (version 9.2; SAS Inc., Cary, NC). Statistical significance was set at $P < 0.05$.

3 | RESULTS

3.1 | Subject characteristics

The characteristics of the 38 children (27 males) who were admitted for asthma attacks are listed in Table 1. The mean age was 9.9 ± 2.6 years. Thirty-one (81.6%) children were diagnosed with asthma prior to the onset of our study. Five (13.2%) patients were prescribed inhaled corticosteroids prior to their asthma attack. Out of the 33 patients, four of them prescribed increased ICS and one a maintenance inhaled corticosteroid dose. Four patients who were prescribed a leukotriene receptor antagonist changed their maintenance treatment to an inhaled corticosteroid, and five patients with poor adherence were retrained for inhaled corticosteroid use. An inhaled corticosteroid was prescribed for the first time in 19 patients, while a leukotriene receptor antagonist was prescribed for the first time in four patients. Dose changes in or new prescriptions of inhaled corticosteroids were conducted after study completion.

TABLE 1 Subject demographics

Characteristics	N = 38
Age, y	9.9 ± 2.6
Sex, male (%)	27 (71.1)
Previously diagnosed asthma, n (%)	31 (81.6)
Current ICS user, n (%)	5 (13.2)
Hospital stay, days	3 (3-4)
Symptom Score (5-15)	
At admission	8.6 ± 1.7
One week after discharge	5.0 ± 0.2
Respiratory virus infection, n (%)	23 (60.5)
Rhinovirus infection, n (%)	21 (55.3)
Influenza virus infection, n (%)	2 (5.3)
Blood eosinophil, / μ L	460 (170-680)
Induced sputum (N = 27)	
Sputum eosinophils, %	3 (0-15)
Sputum eosinophils $\geq$ 3%, n (%)	16 (59.3)
Sputum neutrophils, %	47.6 ± 25.5
Sputum neutrophils $\geq$ 40%, n (%)	16 (59.3)
Total IgE, IU/mL	484 (258-690)
Atopy, n (%)	34 (89.5)
Positive BHR, n (%)	22 (57.9)
PC ₂₀ , mg/mL	9.90 (2.8-49.5)

The values are presented as mean $\pm$ standard deviation, median (interquartile range) or number (%).

ICS, inhaled corticosteroids; BHR, bronchial hyperresponsiveness; PC₂₀, the concentration of methacholine that caused a 20% decrease in FEV₁.

The body temperature of subjects was held at 36.7°C (IQR: 0.5). No significant changes in body temperature were identified during the study period. The mean blood eosinophil count was 460 cells/ μ L (range: 170-680 cells/ μ L). The mean percentage of eosinophils from induced sputum was 3% (range: 0-15%), and the mean total IgE was 484 IU/m (range: 258-690 IU/m). Atopy was observed in 34 (89.5%) children. A respiratory virus was present in 23 (60.5%) patients. The most frequently identified viral pathogen was rhinovirus; the remainder of aspirates positive for viral infection yielded influenza

virus. The EBT was not significantly different between virally infected subjects and non-infected subjects (data not shown). The median hospital stay duration was 3 days. Asthma scores decreased from a mean of 8 points at admission to 5 points at the 1-week follow-up visit after discharge. The median PC₂₀ was 9.85 mg/mL (range: 2.98-49.5 mg/mL).

3.2 | Changes in spirometry before and after treatment

All of the children who experienced asthma attacks had a low predicted percentage of FEV₁. Similarly, the FEV₁/forced vital capacity (FVC) and forced expiratory flow at 25-75% of the vital capacity (FEF_{25-75%}) values obtained at admission were significantly reduced compared with those obtained at 1 week after discharge ($P < 0.001$). Conversely, the mean FEV₁ after BD inhalation was greater at admission than it was at the 1-week follow-up visit ($P = 0.002$) (Table 2).

3.3 | Change in predicted percent of PEFR and PLET over time

The PEFR obtained on day 1 of hospitalization (D1; day of admission) was very low (~56%), but increased to >80% by the third day of hospitalization (D3) ($P < 0.001$). There was also a significant increase in the PEFR from D1 to the follow-up examinations after discharge ($P < 0.001$; Figure 2 and Figure S1). Contrastingly, the PLET, which initially measured 34.1 $\pm$ 0.2°C on D1, decreased to 33.7 $\pm$ 0.2°C on day 4 of hospitalization (D4), and further decreased to 33.3 $\pm$ 0.3°C at 1 month after discharge ($P = 0.0076$; Figure 2 and Figure S1).

3.4 | Correlation between spirometry and PLET at admission

The PLET was higher in children with a positive bronchodilator responsiveness (BDR) than in those without (34.6°C [range: 33.9-34.9°C] vs 33.9°C [range: 33.7-34.3°C], $P = 0.034$; Figure 3). The PLET was positively correlated with the BDR ($r = 0.380$, $P = 0.024$) and inversely correlated with the FEV₁/FVC ($r = -0.361$, $P = 0.033$) (Figure S2). No correlation was observed between the PLET and FEV₁ or FEF_{25-75%}.

TABLE 2 Changes in spirometry before and after treatment in children with asthma attacks

Spirometry	Admission	1 wk after discharge	P-value
FVC, % predicted	75.8 ± 21.1	103.5 ± 14.5	<0.001
FEV ₁ , % predicted	63.3 ± 24.4	99.5 ± 14.1	<0.001
FEV ₁ /FVC, %	69.2 ± 13.0	81.9 ± 6.9	<0.001
FEF _{25-75%} , % predicted	35.7 ± 23.3	71.8 ± 18.6	<0.001
Change in FEV ₁ after BD, %	16.6 ± 14.4	8.0 ± 7.6	0.002

The values are presented as mean $\pm$ standard deviation, median (interquartile range) or number (%).

FEV₁, forced expiratory volume in one second; BD, bronchodilator; FVC, forced vital capacity; FEF_{25-75%}, forced expiratory flow at 25-75% of vital capacity.

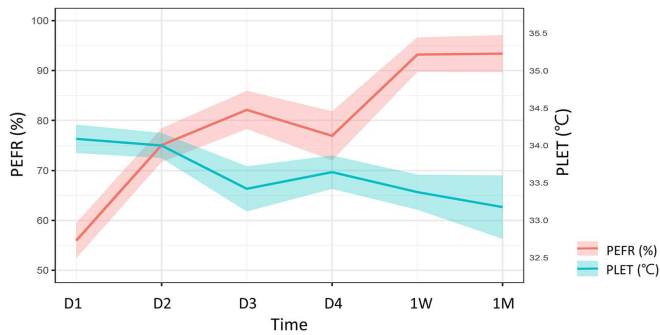


FIGURE 2 Changes in the percentage of predicted peak expiratory flow rate (PEFR) and plateau value at the end of expiration (PLET) over time following an asthma attack. Associated *P* values were obtained using a linear mixed model ($P < 0.0001$ and $P = 0.0076$, respectively). The time-dependent change in the PEFR during the study period significantly affected each subject's PLET during hospitalization and at the 1-month follow-up ($P = 0.005$ and $P = 0.032$, respectively). D1, day 1 of hospitalization; 1W, 1 week after hospital discharge; 1M, 1 month after hospital discharge

3.5 | Changes in FeNO over time

The FeNO at the time of admission, 1 week after discharge, and 1 month after discharge was 21.74 ± 3.3 ppb, 21.1 ± 4.6 ppb, and 31.35 ± 4.4 ppb, respectively. No significant time-dependent changes were identified (Figure S3).

3.6 | Association between PLET and PEFR over time

Results of the analyses investigating potential dynamic relationships between the PLET and time-dependent covariates (PEFR, asthma score, and FeNO) are presented in Table 3. During hospitalization (D1–D4), changes in the PLET over time were significantly associated with PEFR changes in individual children and amongst the entire cohort. Meanwhile, Changes in the PLET over time were significantly

associated with PEFR changes in individual children during the study period (D1 to 1 month after discharge) (Figure 1 and Figure S1). However, changes in PLET over time were not significantly associated with FEV₁ changes in individual patients and amongst the entire cohort (Supplementary Table S1). Meanwhile, changes in the FeNO value and asthma score over time did not affect the PLET in individual children or amongst the entire study population.

3.7 | Relationships among the sputum eosinophil count, PLET, and FeNO

We did not identify a significant correlation between the eosinophil count and PLET ($\rho = -0.107$, $P = 0.609$) or between the eosinophil count and FeNO value ($\rho = -0.114$, $P = 0.596$) or between PLET and FeNO values ($\rho = -0.262$, $P = 0.155$) at admission. Meanwhile, a negative correlation was observed between all PLET and FeNO values measured from all time points: after admission and at 1 week and 1 month after discharge ($\rho = -0.311$, $P = 0.007$).

4 | DISCUSSION

Our study shows that the PLET was elevated when children initially presented with an asthma attack and decreased over time with treatment. The PLET was correlated with the BDR and FEV₁/FVC. During the course of recovery, the PLET decreased as the PEFR increased, indicating that the PLET is dynamically associated with the PEFR over time. However, the PLET was not correlated with the FeNO value in children with asthma attacks.

Many studies have explored the association between the EBT, airway inflammation, and vascular and fibrous remodeling of airways in children with asthma.⁶ In the present study, PLET levels were highest at admission, when airway inflammation was expectedly the most prevalent, thus supporting previous literature linking increased EBT with poorly controlled asthma and decreased EBT following anti-inflammatory treatment.^{20,22}

As rhinovirus is known to be the main cause of acute asthma exacerbations, rhinovirus was unsurprisingly detected in the majority of our subjects.^{29–31} The EBT is known to increase with viral infections.⁶ However, we did not detect a difference in the PLET between virally infected children and those without evidence of a viral illness.

Here, the PLET was higher in children with BDR than in those without BDR; additionally, the PLET was correlated with changes in the FEV₁ after BD. BDR is known to be a surrogate marker of airway inflammation and airway remodeling and can predict the response to inhaled corticosteroids.³² In our study, the EBT was also correlated with the FEV₁/FVC at admission, which is an index of airway obstruction and inflammation. Therefore, the current study suggests that the EBT, as measured by the PLET, may adequately reflect airway inflammation in children with asthma attacks.

Some studies have shown a significant association between the EBT and FeNO value, a typical marker of airway inflammation, in

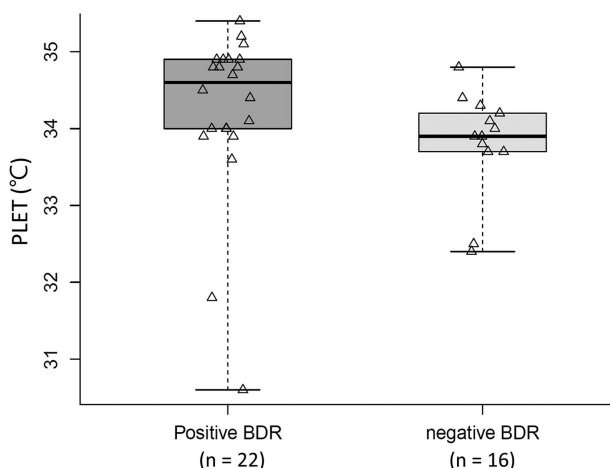


FIGURE 3 Association of exhaled breath temperature (EBT) with bronchodilator responsiveness (BDR). Plateau values at the end of expiration were higher in children with positive BDR than in patients without BDR ($P = 0.034$)

TABLE 3 Association between PLET and time dependent covariate (TDC)

Variable	Between subject effect		Within subject effect	
	Beta (SE)	P-value	Beta (SE)	P-value
PEFR (D1-D4)	-0.024 (0.01)	0.018	0.018 (0.006)	0.005
PEFR (D1-1M)	-0.015 (0.01)	0.135	0.012 (0.005)	0.032
Asthma score (D1-D4)	0.138 (0.241)	0.570	-0.039 (0.162)	0.810
Asthma score (D1-1M)	0.137 (0.220)	0.535	-0.038 (0.155)	0.807
FeNO	0.018 (0.02)	0.386	-0.027 (0.015)	0.105

PEFR, peak expiratory flow rate; D1, hospital day 1; 1M, one month; FeNO, fractional exhaled nitric oxide.

children with asthma.²¹ However, in the current study, unlike the EBT, no consistent changes in the FeNO levels with time were noted following an asthma attack. However, when all of the EBT and FeNO values measured after admission and at 1 week and 1 month after discharge were compared, a negative correlation between EBT and FeNO was identified. This suggests that while the EBT gradually decreases following asthma attacks, the FeNO level temporarily decreases owing to systemic steroid use during hospitalization, and then increases again after discharge. Piacentini and colleagues³³ found a significant positive correlation between EBT, FeNO, and eosinophils in induced sputum samples. However, in our study, eosinophil counts in the induced sputum were not correlated with either the EBT or FeNO. Although FeNO concentrations are known to correlate with eosinophilic airway inflammation, the measured level of eosinophilic inflammation does not always correlate with symptoms and pulmonary function.⁶ Other non-eosinophilic airway inflammation (ie, neutrophilic inflammation) may be present in severe asthma,⁶ as evidenced in our study cohort. Although the relationship between subjective asthma symptoms and objective measures of airway inflammation has been explored in-depth, there have been no significant associations discovered between the EBT and parameters of type 2 inflammation (ie, FeNO or sputum eosinophil counts) that can be used to assess the risk of an asthma exacerbation.³³ Nevertheless, the EBT may correlate with other types of inflammation.⁶

While the PLET was not correlated with the FeNO level or asthma score in the present study, the decrease in PLET over time was correlated with an increased PEFR over time. This suggests that the PLET is as useful as the PEFR, which has been used to detect changes or trends in a patient's level of asthma control and is believed to reflect the progressive decline in airway obstruction over time following an asthma attack. Therefore, the easily measurable EBT may be useful for estimating changes in airway inflammation that occur during recovery after an asthma attack.

Some limitations of this study should be noted. First, we were unable to include all children who experienced an asthma attack during the study period, as some patients were unable to perform the necessary respiratory tests owing to the severity of their asthma attacks, and were thus excluded. Second, the PLET and PEFR were not measured at the same time each day during hospitalization because the first measurement was obtained immediately following admission. Therefore, our results may have been affected by the patients' diurnal

rhythms. Finally, the association between sputum eosinophil counts and PLET was not assessed longitudinally, as sputum eosinophil counts were measured only immediately after admission.

The main strength of our study was that it longitudinally measured the PLET in children who experienced asthma attacks from their initial admission until 1 month after discharge. This is the first study to sequentially measure the EBT at three distinct stages, namely the onset of an asthma attack, during the recovery period, and after patients achieved a stable state; the present study is also the first to compare subjects' symptomatology and pulmonary function during these same three time periods.³⁴⁻³⁶

In conclusion, this study showed that the EBT can be used to assess a pediatric patient's recovery from an asthma attack. Therefore, children with asthma attacks should be encouraged to use exhaled breath thermometers to clinically aid in the maintenance of asthma control and in therapeutic management. We suggest that EBT follow-up may be useful for monitoring asthma in children.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplements

Supplementary Figure 1.

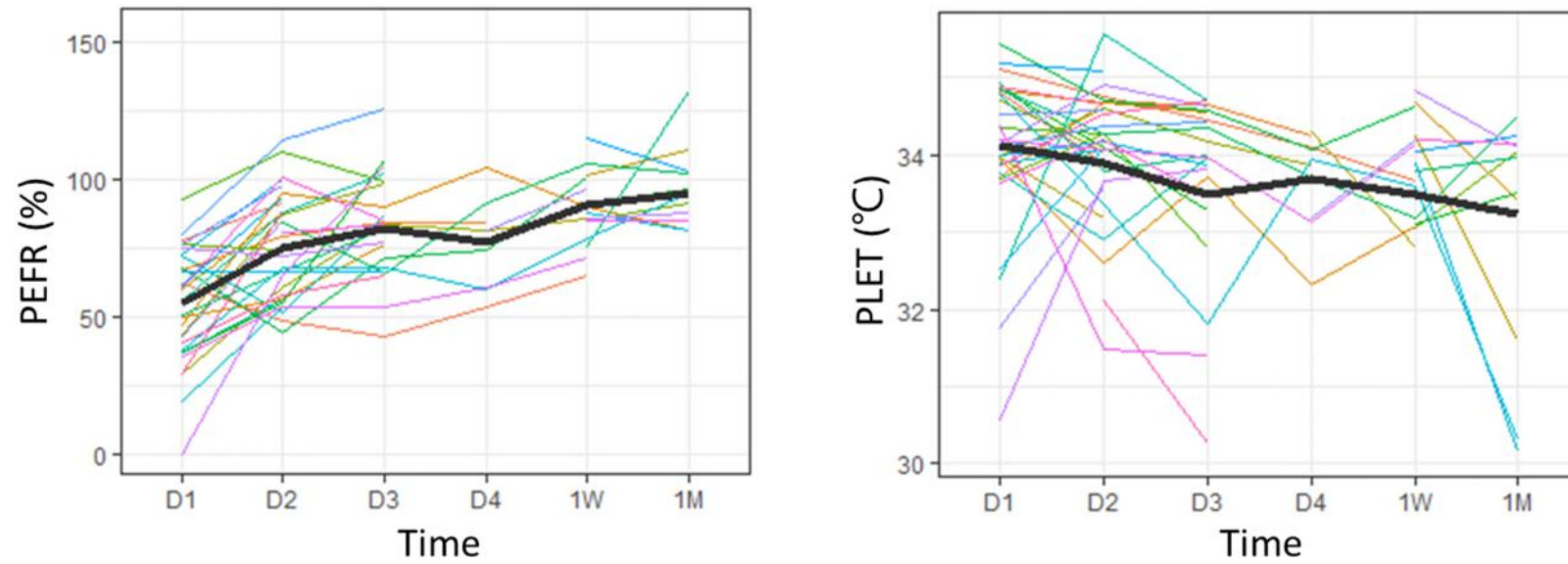


Fig. S1. Change of percentage of predicted peak expiratory flow rate (PEFR) and plateau values at the end of expiration (PLET) over time after asthma attacks in all subjects.

Supplementary Figure 2.

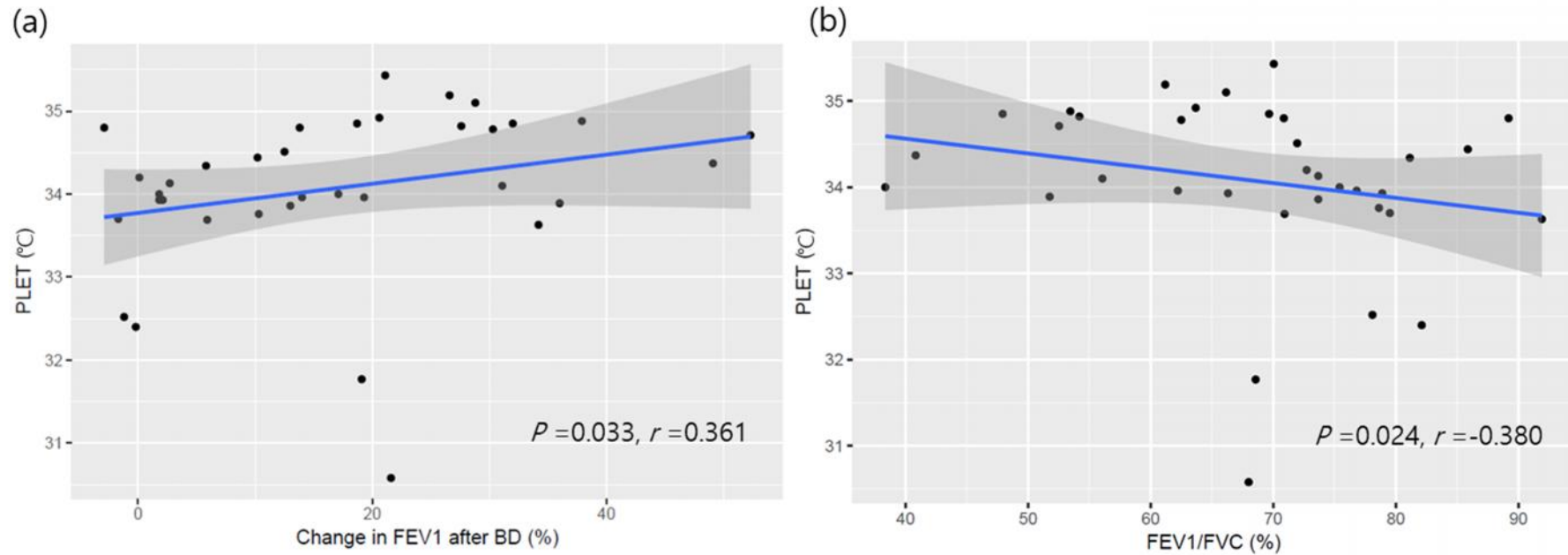


Fig. S2. Plateau values at the end of expiration (PLET) had a positive correlation with bronchodilator response (BDR) and an inverse correlation with forced expiratory volume in one second (FEV_1) / forced vital capacity (FVC) in patients with asthma attacks ($r = 0.380$, $P = 0.024$ and $r = -0.361$, $P = 0.033$).

Supplementary Figure 3.

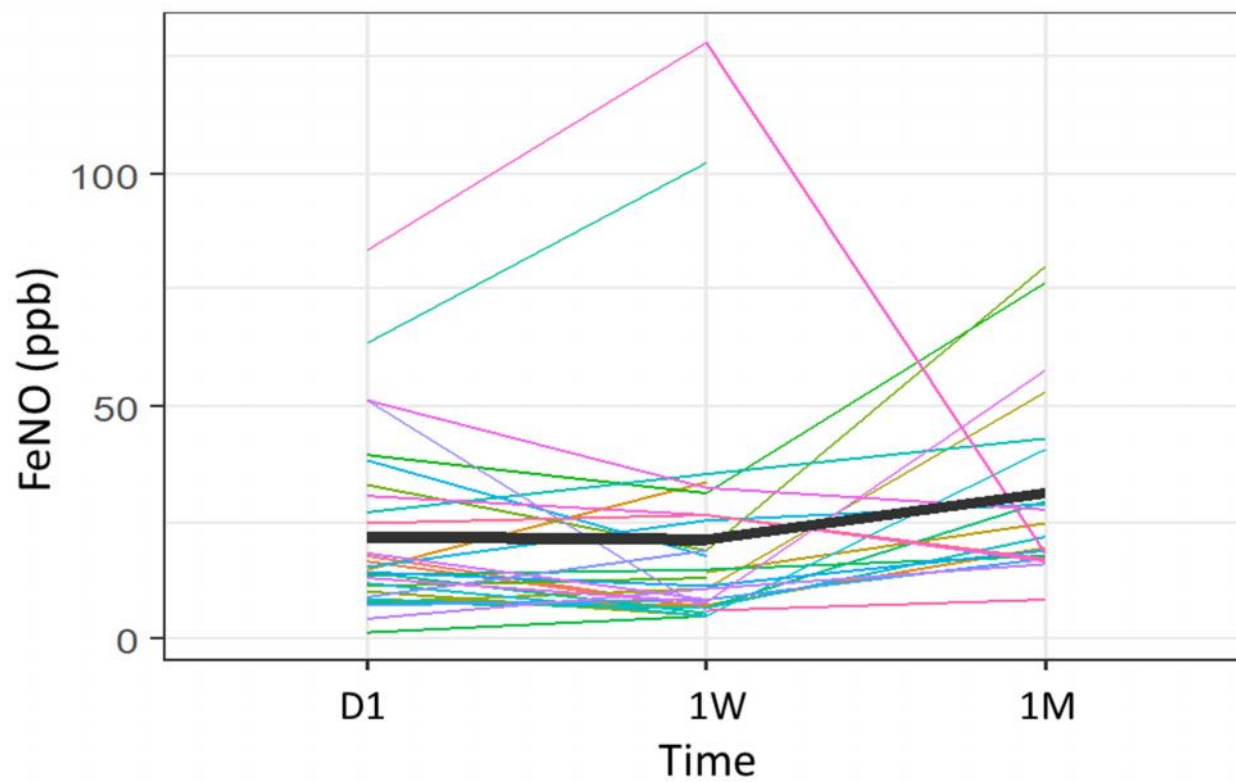


Fig. S3. The changes in fractional exhaled nitric oxide (FeNO) measured from admission to outpatient visit one month following discharge in each subject. There was no significant time-dependent change

Supplementary Table 1. Association between PLET and FEV₁ over time

	FEV ₁	
	beta (SE)	<i>P</i> -value
TDC (between)	-0.002 (0.013)	0.8875
TDC (within)	-0.003 (0.009)	0.7098

PLET, plateau value at the end of the expiration; FEV₁, forced expiratory volume in 1 s; SE, standard error; TDC, time dependent covariate