

Exhaled Breath Temperature Measurement and Asthma Control in Children Prescribed Inhaled Corticosteroids: A Cross Sectional Study

Laura Hamill, MB, BCH,^{1*} Kathryn Ferris, MB, BCH,^{1*} Kirsty Kapande, MB, BCH,^{1*}
 Laura McConaghy, MB, BCH,¹ Isobel Douglas, RCN,² Vincent McGovern,²
 and Michael D. Shields, MB, ChB, MD^{1,2}

Summary. Background: Exhaled breath temperature (EBT) reflects airways (both eosinophilic and neutrophilic) inflammation in asthma and thus may aid the management of children with asthma that are treated with anti-inflammatory drugs. A new EBT monitor has become available that is cheap and easy to use and may be a suitable monitoring device for airways inflammation. Little is known about how EBT relates to asthma treatment decisions, disease control, lung function, or other non-invasive measures of airways inflammation, such as exhaled nitric oxide (ENO). Objective: To determine the relationships between EBT and asthma treatment decision, current control, pulmonary function, and ENO. Methods: Cross-sectional prospective study on 159 children aged 5–16 years attending a pediatric respiratory clinic. EBT was compared with the clinician's decision regarding treatment (decrease, no change, increase), asthma control assessment (controlled, partial, uncontrolled), level of current treatment (according to British Thoracic Society guideline, BTS step), ENO, and spirometry. Results: EBT measurement was feasible in the majority of children (25 of 159 could not perform the test) and correlated weakly with age ($R = 0.33$, $P = <0.01$). EBT did not differ significantly between the three clinician decision groups ($P = 0.42$), the three asthma control assessment groups ($P = 0.9$), or the current asthma treatment BTS step ($P = 0.57$). Conclusions & Clinical Implications: EBT measurement was not related to measures of asthma control determined at the clinic. The routine intermittent monitoring of EBT in children prescribed inhaled corticosteroids who attend asthma clinics cannot be recommended for adjusting anti-inflammatory asthma therapy.

Key words: breath; temperature; asthma; child.

INTRODUCTION

Asthma management in children is currently guided by symptoms and aided by lung function measurement in older children. Inhaled corticosteroids act by dampening airways inflammation and have become the main form of anti-asthma therapy.¹ Despite asthma being a chronic inflammatory airways disease, we do not routinely assess inflammation and adjust therapy on its presence or extent. Eosinophilic inflammation persists in the airways of children with mild, moderate, and severe classical atopic asthma and can be non-invasively measured by using exhaled nitric oxide (ENO).^{2–5} Despite this, the use of ENO has not been shown in all studies to be helpful in the longitudinal monitoring of childhood asthma.^{6,7} This apparent lack of utility of ENO may be because eosinophilic inflammation is not the sole or only driver underlying the symptoms of asthma. It could also be that ENO values need to be interpreted in light of the recent medication adherence, which can be difficult to assess. Induced sputum eosinophil count has been used to guide asthma therapy in adults but has been less well studied in

children and given its practical difficulties and lack of immediately available results, it is unlikely to enter routine

¹Centre of Infection & Immunity, Queen's University Belfast, Northern Ireland, UK.

²Royal Belfast Hospital for Sick Children, Belfast Health Social Care Trust, Belfast, Northern Ireland, UK.

Laura Hamill, Kathryn Ferris, and Kirsty Kapande are the joint first authors.

Funding source: none reported.

*Correspondence to: Michael D. Shields, Centre for Infection & Immunity, Health Sciences Building, Queen's University Belfast, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland, UK. E-mail: m.shields@qub.ac.uk

Received 1 June 2014; Revised 6 January 2015; Accepted 15 January 2015.

DOI 10.1002/ppul.23204
 Published online in Wiley Online Library
 (wileyonlinelibrary.com).

clinical practice. Other simple ways of measuring the underlying airways inflammation in asthma are needed.

Recently, exhaled breath temperature (EBT) has been hypothesized to reflect the extra heat produced from underlying airways inflammation in asthma and in particular its increased vascularity.^{8–12} The temperature of blood in the bronchial wall vasculature deep within the lungs represents core body temperature and heat is transferred out into the inspired air. EBT is not simply another measure of body temperature and does not correlate with ear canal and axillary temperatures, which themselves are closely correlated.^{8–12} Detectable increases in EBT have been shown to herald the onset of viral-induced asthma exacerbations in children and are seen in exercise challenges in both children with asthma and children without asthma.^{14–16} Whereas exhaled nitric oxide levels relate closely to eosinophilic airways inflammation, EBT is likely to be related to all types of inflammation, including neutrophilic inflammation. Neutrophil inflammation has recently been associated with severe asthma that is unresponsive to inhaled corticosteroids (ICS).¹³ Popov et al. described a specifically designed portable device for the measurement of EBT, which is now commercially available. Each exhalation the patient makes increases the temperature inside the reservoir chamber until temperature equilibrium is reached. The EBT measurement can be made with precision and is highly repeatable.¹³ Previous research suggests that EBT may be associated with age in childhood, lung volume, and room temperature.^{17,18} With the recent availability of a cheap, easy to use handheld EBT device and studies showing that daily monitoring of EBT parallels other indices of asthma control, it is important to further evaluate its role as a measurement in an outpatient pediatric setting. For EBT to become a useful adjunct to the clinical management of childhood asthma, its relation to current asthma control and treatment needs to be further clarified.

The aim of this study, therefore, was to examine a group of children with asthma (mostly on inhaled corticosteroids) attending a respiratory pediatrics outpatient clinic and to determine the relationships between EBT, current asthma control and treatment, pulmonary function, ENO, and the clinician's decision regarding future management.

METHODS

Participants

Consecutive children with asthma (aged 5–16 years) attending the respiratory clinic in the Royal Belfast Hospital for Sick Children (RBHSC) were recruited within the time constraints of the clinic session. All assessments were conducted between 9 AM and 1 PM to minimize potential diurnal variation. Children with

current head colds, chest infections, or asthma exacerbations were not included. The physicians (MDS, VMcG), who were blinded to the EBT measurements, clinically assessed all subjects. Parental written informed consent or child assent where appropriate was obtained and the study was approved by the Office of Research Ethics Committees for Northern Ireland.

Subjects had been diagnosed with asthma by a physician (MDS, VMcG) and all had a history of recurrent wheezing (e.g. precipitated by respiratory infection, exercise, or exposure to allergens) and more than two-thirds had atopic disease (eczema, allergic rhinitis) or other allergies, including food allergy. After taking a detailed respiratory history, recording of lung function, and ENO value, the children were classified according to how well the asthma was controlled. The physician then made a decision as to whether asthma treatment was to be altered. The physicians' primary aim in asthma management was to try to control children's asthma at the lowest acceptable dose of inhaled corticosteroids.

The physicians then classified each child's asthma control according to the following broad general categories: controlled (no nocturnal waking, infrequent short acting beta 2 agonist use e.g. <2 puffs/week, occasional mild symptoms, e.g. with exercise and no exacerbations in last 3 months), partially controlled (nocturnal waking <3 nights/week, beta 2 agonist use, e.g. <4 puffs/day, mild limitation in exercise tolerance due to asthma, and 2 or fewer mild exacerbations in the previous 3 months), or uncontrolled (nocturnal waking 4–7 nights/week, beta 2 agonist use, e.g. >5 puffs/day, limitation in exercise tolerance due to asthma and/or significant asthma exacerbations requiring oral steroid, Emergency Department attendance, or hospital admission in the previous 3 months).

The physician's decision, on the basis of clinical history, examination, pulmonary function, and ENO record (if available) as to whether treatment should be decreased, unchanged or increased was recorded.

Current asthma medications were recorded and subjects were classified according to the British Thoracic Society (BTS) treatment stages.¹ This variable (BTS-step) and the physician's decision to alter therapy took into account and adjusted for the current level of adherence as reported by either the parent or child.

Exhaled Nitric Oxide (ENO)

ENO was measured before spirometry using the handheld NObreath[®] (Bedfont Scientific Ltd., Kent, UK) as per manufacturer's instruction and as previously described.¹⁹ The average of two maneuvers was recorded.

Spirometry

Forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), and the ratio FEV1/FVC were measured

using the MicroLab (CareFusion, Rolle, Switzerland) according to the ERS standards and with the child friendly visual incentive screen on. Percent predicted values were reported, which take into account gender, age, and height.

Exhaled Breath Temperature (EBT)

EBT was measured using the commercially available handheld device, X-Halo[®] (Delmedica, Singapore). In addition, the time to temperature equilibration was recorded. In brief, the children were asked to inhale through the nose and exhale into the X-Halo device using normal tidal breathing. The children breathed continuously into the thermal chamber until the central heat sink reached a temperature plateau. Each exhalation increases the temperature inside the reservoir chamber until temperature equilibrium is reached. The thermal sensor in the device is claimed to be accurate to 0.03 °C.

Analysis

Descriptive data were reported as mean (SD) or median (IQR, range) as appropriate. Lung function and ENO distributions (after log transformation) were normal and parametric comparative statistics were used (ANOVA). As the distribution of EBT was mildly skewed to the left, between group comparisons of EBT were made using Kruskal–Wallis tests. If the ANOVA or Kruskal–Wallis test showed statistically significant results, post-hoc tests were then performed to determine which groups were different. Correlations were made using either Pearson's or Spearman's correlation coefficients (R) where appropriate. Two repeated EBT maneuvers were recorded in a subgroup of cases and repeatability was reported as the mean difference between the two measurements, intra-class correlation coefficient (ICC), and 95% limits of agreement. A *P*-value less than 0.05 indicated statistical significance. JMP[®] version 11 (SAS Institute, Inc., Cary, NC) statistical software was used.

Sample Size

A sample size of greater than 100 participants was calculated to give a 2-sided 95% confidence interval of 0.45–0.71 for an observed correlation of 0.6 between FeNO and EBT if such a correlation existed.¹³

RESULTS

We recruited 159 children (60% male), aged between 5 and 16 years (median: 10 years, IQR: 7–13 years). The majority of the children had other clinical atopic disease (eczema, allergic rhinitis) or food allergies. Twenty-five children, mostly less than 7 years of age, were unable to adequately perform the EBT test with the commonest reason for failure being an inability to continue until temperature equilibrium was obtained;

results from 134 children are reported. The distribution of the time taken to make the EBT measurement (time to temperature equilibration) ranged from 1.02 to 8.4 min (median 3.22 min, IQR: 2.02–4.60 min). Room temperature ranged between 24.30 and 25.8 °C and did not correlate with EBT (correlation coefficient $R = -0.02$). The distribution of EBT was mildly skewed to the left and values ranged between 27.23 and 35.16 °C (median: 33.76 °C, IQR: 31.80–34.23 °C).

EBT was weakly positively correlated with age (correlation coefficient $R = 0.33$, $P < 0.01$) and with lung volume (FVC, $R = 0.34$, $P < 0.01$). No correlation was observed between EBT and lung volumes when expressed as percentage predicted (FVC%, $R = 0.08$, $P < 0.4$). Children's ages were similar in the grouping variables (physician's decision, control).

Fourteen children were only taking when required beta 2 agonists (BTS step 1), 17 children were on low-dose inhaled corticosteroids ($\leq 400 \mu\text{g/day}$ of ICS; BTS step 2), 44 children were on moderate-dose ICS (400–800 $\mu\text{g/day}$) combined with a long acting beta 2 agonist (LAB2A) (BTS step 3), 38 were on high-dose ICS ($> 800 \mu\text{g/day}$) and LAB2A and/or a leukotriene antagonist (LTA, BTS step 4), and 21 children were requiring additional oral steroids or anti-IgE therapy (BTS step 5).

Physician's Decision Regarding Future Treatment

EBT levels for the three treatment decision groups (treatment decreased, unchanged, increased) are shown in Table 1. When EBT levels were compared across the 3 groups, there was no difference between EBT (decrease: median = 32.42 °C [IQR: 31.23–34.23 °C] versus no change: median = 33.82 °C [IQR: 32.08–34.27 °C] versus increase: median = 33.69 °C [IQR: 31.04–34.23 °C], $P = 0.42$, Fig. 1).

EBT and Asthma Control

EBT levels for the three asthma control groupings (controlled, partially controlled, uncontrolled) are shown in Table 1. When EBT levels were compared across the three groups, there was no statistically significant difference between EBT (controlled: median = 33.52 °C [IQR: 31.42–34.23 °C] versus partially controlled: median = 33.79 °C [IQR: 32.11–34.23 °C] versus uncontrolled: median = 33.79 °C [IQR: 32.12–33.79 °C], $P = 0.9$, Fig. 2).

EBT Levels and Current Asthma Treatment (BTS step)

Although EBT was the highest in those on BTS step 5 treatment when the EBT levels were compared across the BTS treatment subgroups, there was no statistical difference found ($P = 0.57$, Table 1 and Fig. 3).

TABLE 1—Summary of EBT, ENO and spirometry by BTS-step, by treatment decision and by asthma control.

	EBT (°C) median (IQR), range	ENO (ppb) median (IQR), maximal value	FEV1 (% predicted) mean (SD)	FVC (% predicted) mean (SD)	FEV1/FVC ratio mean (SD)
By BTS-step					
Step 5 N = 21	34.11 (33.40–34.34), 28.49–35.16	25 (11–53), 300	82 (13)	89 (13)	0.78 (0.08)
Step 4 N = 38	33.80 (32.07–34.19), 27.40–34.88	6 (2–16), 230	91 (14)	92 (12)	0.85 (0.1)
Step 3 N = 44	33.73 (32.29–34.20), 28.25–34.75	7 (2–26), 129	94 (19)	93 (14)	0.87 (0.1)
Step 2 N = 17	33.11 (30.87–34.23), 28.15–34.82	8 (4–48), 106	86 (19)	86 (18)	0.84 (0.08)
Step 1 N = 14	33.48 (30.92–34.23), 27.23–34.71	9 (3–31), 106	90 (13)	88 (14)	0.86 (0.07)
<i>P</i> -value (post-hoc comparative difference)	<i>P</i> = 0.57	<i>P</i> = <0.01 (BTS step 5 > other BTS steps)	<i>P</i> = 0.1	<i>P</i> = 0.4	<i>P</i> < 0.01 (BTS step 5 has lower value than all other BTS steps)
By treatment decision					
Increase N = 40	33.69 (31.04–34.23), 28.25–34.78	26 (7–59), 300	88 (19)	89 (15)	0.84 (0.1)
No change N = 83	33.82 (32.08–34.27), 27.23–34.88	7 (1–16), 230	91 (17)	91 (14)	0.85 (0.1)
Decrease N = 11	32.42 (31.23–34.23), 29.65–34.23	6 (4–13), 25	92 (10)	90 (12)	0.87 (0.05)
<i>P</i> -value (post-hoc comparative difference)	<i>P</i> = 0.42	<i>P</i> = 0.0025 (increase > no change)	<i>P</i> = 0.65	<i>P</i> = 0.72	<i>P</i> = 0.8
By asthma control					
Uncontrolled N = 35	33.79 (32.12–33.79), 28.25–35.16	25 (5–59), 190	87 (20)	90 (15)	0.82 (0.1)
Partial control N = 47	33.79 (32.11–34.23), 27.40–34.47	13 (4–30), 300	89 (19)	93 (12)	0.84 (0.08)
Controlled N = 52	33.52 (31.42–34.23), 27.23–34.88	5 (1–13), 72	92 (16)	90 (15)	0.87 (0.07)
<i>P</i> -value (post-hoc comparative difference)	<i>P</i> = 0.9	<i>P</i> < 0.001 (uncontrolled > Controlled)	<i>P</i> = 0.4	<i>P</i> = 0.6	<i>P</i> = 0.1

EBT (°C) and ENO (ppb) are displayed as median (IQR, range) and FEV1 (%), FVC (%), and ratio FEV1/FVC are displayed as mean (SD). EBT, exhaled breath temperature, ENO, exhaled nitric oxide, FEV1, forced expiratory volume in 1 sec, FVC, forced vital capacity. Lung function values are expressed as percentage predicted for age and gender. Post-hoc testing was performed if the ANOVA or Kruskal–Wallis test *P*-value was close to or below 0.05.

EBT levels and ENO and spirometry

EBT did not correlate closely with either Log ENO ($R = 0.06$, $P = 0.6$, Table 1 and Fig. 4) or with any of the spirometry indices (FEV1 [%]: $R = 0.06$, FVC [%]: $R = 0.14$, Ratio FEV1/FVC: $R = -0.09$)

Log ENO levels were statistically higher in children where the therapy was increased compared to either no change or decrease ($P < 0.05$), and was higher for those with uncontrolled compared to controlled asthma ($P < 0.05$). In addition, ENO was higher for those on BTS-step 5 ($P < 0.05$).

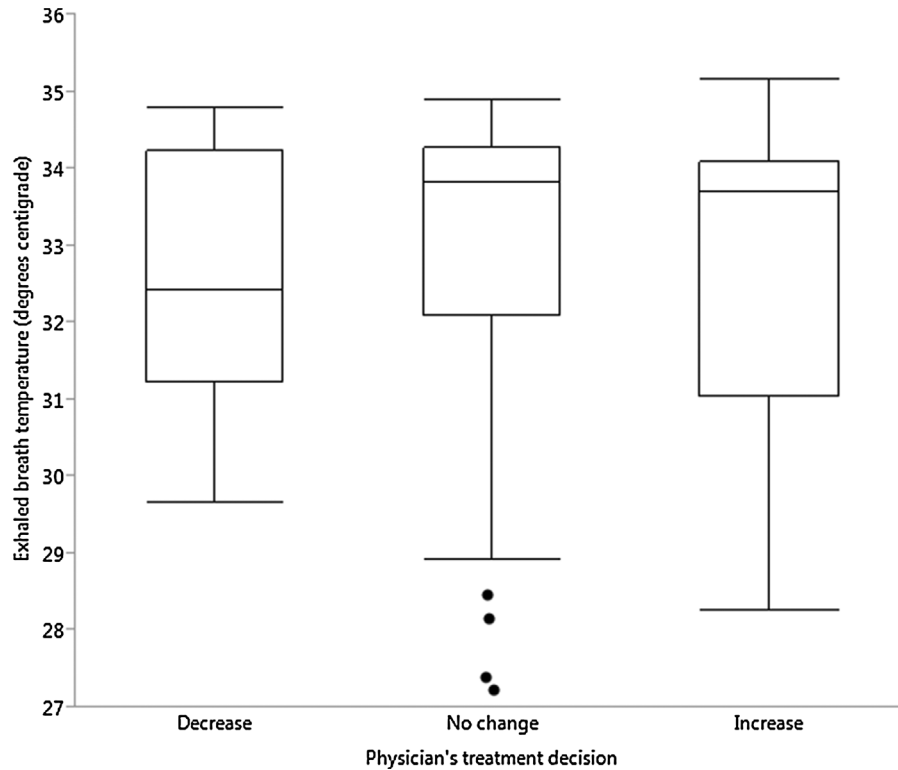


Fig. 1. Box and whisker plots of EBT (°C) according to physician's treatment decision. The whiskers were set at the upper or lower quartile $\pm 1.5 \times \text{IQR}$ and dots are outliers. IQR is the interquartile range.

The ratio FEV1/FVC was lower for those on BTS-step 5 ($P = 0.007$). However, the ratio FEV1/FVC measurement did not differ according to the physician decision or asthma control.

Repeatability of EBT measurement

Nineteen patients performed two repeated EBT maneuvers. The mean difference between the two measurements was 0.15°C ($P = 0.6$), intra-class correlation coefficient (ICC) = 0.98, 95% limits of agreement -1.3 to 1.0°C . When the results of one child's paired measurements were excluded (very poor agreement) the 95% limits of agreement reduced to -0.59 to 0.47 and the ICC was 0.99 indicating very good repeatability.

DISCUSSION

We and others have previously shown that ENO is a non-invasive marker of eosinophilic airways inflammation and that ENO levels are strongly related to the clinical features of childhood asthma and the clinical decision-making process.⁵ However, ENO measurements have not yet been integrated into clinical management strategies since the added value is still uncertain.^{6,7} ENO concentrations seem to correlate with eosinophilic airways inflammation but the level of eosinophilic inflammation

does not always correlate with symptoms and lung function. Indeed, other non-eosinophilic airway inflammation may exist as in neutrophilic inflammation in severe asthma. Increased EBT is thought to relate to the extra heat produced by the increased bronchial wall blood flow and should reflect any type of inflammation. As treatment guidelines recommend the use of anti-inflammatory medications for the control of asthma, our hypothesis was that eliciting the relationship between EBT levels, asthma control, and treatment may indicate what role, if any, EBT measurement could play in the clinical management of asthma.

In this study, we found that the majority of children with asthma and some as young as 5 years old were able to use the X-Halo[®] (Delmedica, Singapore) EBT measuring device. The commonest reason for failure related to an inability of some children to continue the test until temperature equilibrium had occurred. Some successful tests took longer than 8 min of tidal breathing before temperature equilibration occurred. Newer versions of the X-Halo EBT will have reduced this time. We were able to confirm that EBT increased with age in children with asthma and with also with the absolute values of lung function (FVC) and this increase was similar at all levels of asthma treatment or control. However, the magnitude of the age effect we observed

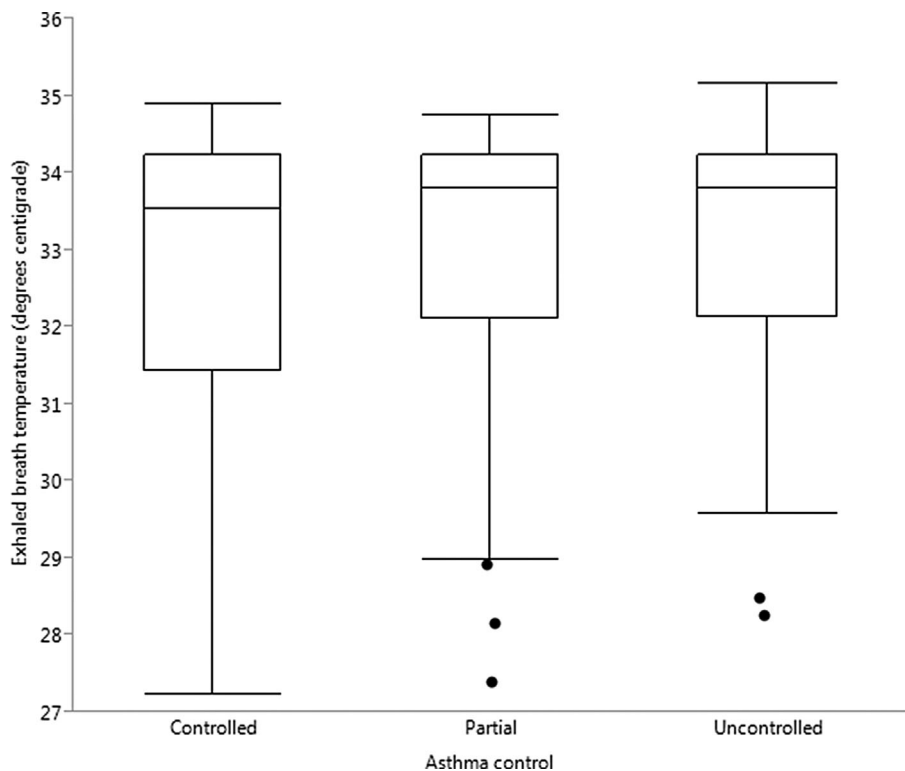


Fig. 2. Box and whisker plots of EBT (0C) according to assessment of asthma control. The whiskers were set at the upper or lower quartile $\pm 1.5 \times \text{IQR}$ and dots are outliers. IQR: interquartile range.

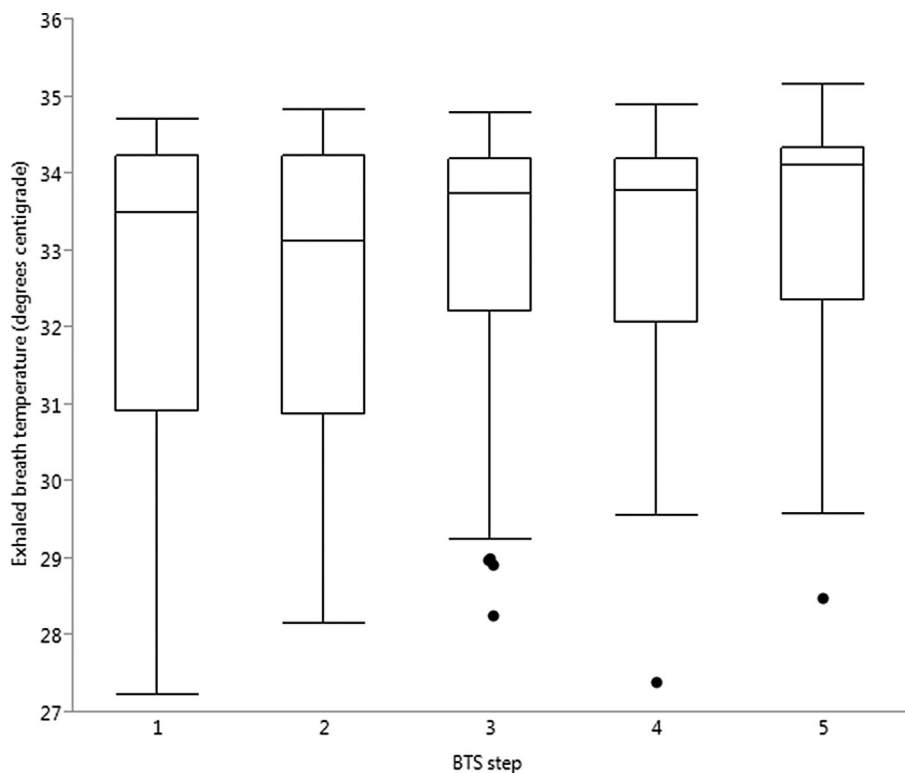


Fig. 3. Box and whisker plots of EBT (0C) according to BTS-step treatment. The whiskers were set at the upper or lower quartile $\pm 1.5 \times \text{IQR}$ and dots are outliers. IQR: interquartile range.

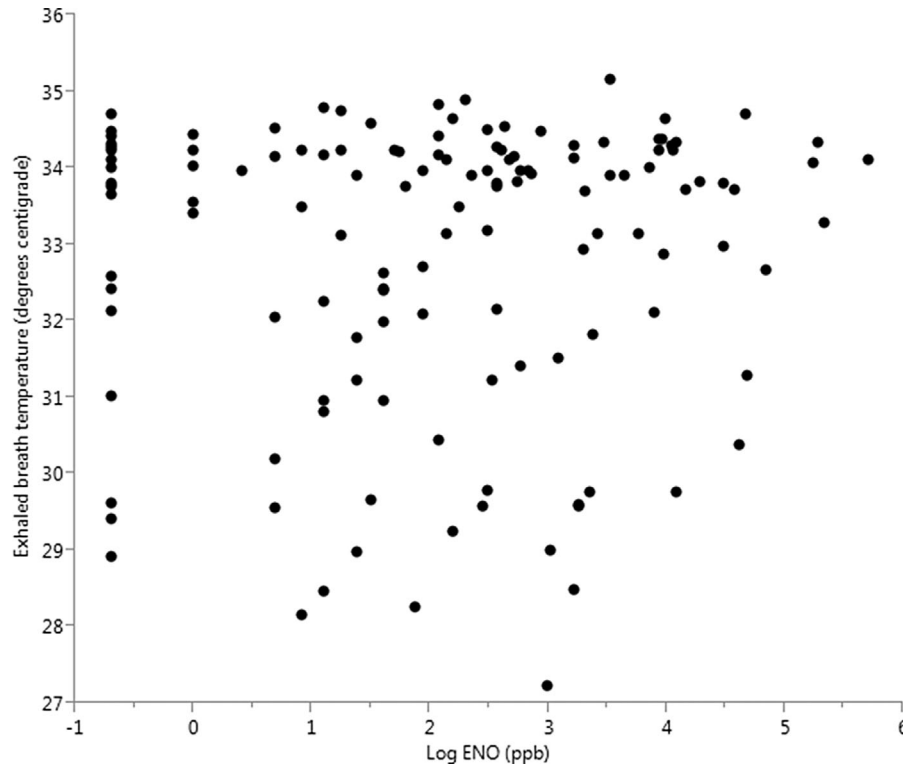


Fig. 4. Scattergram of EBT (0C) versus Log ENO.

($R=0.34$) while statistically significant is much smaller than that reported by Kralimarkova et al. who reported a correlation of $R=0.75$.¹⁷ Although lung volume is related to age, we did not find any relationship between EBT and lung volumes when they were expressed as percentage predicted for age and gender, a previously reported association.^{17,18} EBT measurement correlated weakly with raw lung volumes (FVC) but not with any lung volumes when expressed as a percentage predicted. This suggests that larger lung volumes are associated with increased EBT rather than abnormalities of airway caliber. In addition, in general, lung function testing is not a good marker of asthma control.

In addition, we observed no correlation between EBT and room temperature. However, our clinic temperature range was limited between 24.3 and 25.8 °C.

The first area addressed in this study was relating the EBT levels to the physician's decision regarding future treatment and the assessment of current asthma control. The main finding of our study is that EBT measurements in a large group of asthmatic children did not relate to the clinical decision to alter treatment or to the assessment of current asthma control.

The decision regarding whether a child with asthma's medication should be decreased, unchanged, or increased is based on the clinical assessment of symptoms, physical examination, and where possible on objective measures, such as spirometry. Differences between the decision to

change treatment and asthma control related to the physicians perceived risk of future exacerbation (for example, a children whose asthma was controlled over the summer months would not have had his treatment reduced if seen at the clinic at the start of a potentially bad season). Hence, this decision can be regarded as a sensitive indicator of the physician's conclusions regarding the current disease control and potential risk for any given child. Although the study was not designed with the appropriate blinding to study differences in ENO between well and poorly controlled asthma, we note that ENO is higher in children attending the asthma clinic with poorly controlled asthma when the clinician decided to increase therapy.⁵ During the course of this study, some children and their parents admitted to non-adherence to prescribed inhaled corticosteroid therapy and we classified such children, BTS-step 1 as they had asthma but were on no ICS treatment. Non-adherence to asthma therapy is common, is typically hidden from the physician, and has the ability to interfere with how tests are interpreted. For example, a high EBT or ENO could mean ongoing airways inflammation despite treatment or perhaps more likely non-adherence to current treatment. To overcome this problem would require the use of an electronic dose recorder within the inhaler or directly observed therapy so that test results could be interpreted in the light of very recent adherence. Another potential reason why we did not find a close relationship between

EBT and asthma control may relate to the variable amount of excessive mucus that children with asthma have in their airways. Cystic fibrosis, a condition with intense airways neutrophilic inflammation is associated with low EBT values.²⁰ The large blankets of thick mucus covering the airway walls may prevent heat exchange from the inflamed bronchial wall and the gas exchanged with breathing. We also acknowledge that a close relationship between EBT and asthma control may not have been identified as EBT may only be a useful measurement in particular asthma phenotypes but not all.

We found that EBT was the highest in children who were at Step 5 BTS; however, this was not statistically elevated (Table 1). This group of children with severe asthma may have increased neutrophilic inflammation that may be less responsive to ICS. However, the same children had statistically significant elevated ENO, suggesting eosinophilic airway inflammation was present.

Our study was cross-sectional in nature and therefore only provides information about how EBT relates to areas of asthma assessment at each clinic snapshot view. Much of the previous reported research on EBT has been with serial repeated measurements on the same individuals.²¹ Svensson et al. showed that EBT increased with exercise and remained elevated in children with asthma whose FEV1 dropped by more than 10%.²² Similarly, Peroni et al. reported that the decrease in FEV1 after exercise correlated mildly with EBT (correlation coefficient $R = 0.44$).²³ Further research is, therefore, needed in prospective trials with a patient group adjusting anti-inflammatory therapy according to daily changes in EBT and compared to a group using standard symptom based therapy.

EBT is known to increase with viral infections. A limitation to our study is that we didn't record a precise time interval since the most recent viral infection and when the EBT record was made. The children studied were stable with no obvious current viral infections or asthma exacerbations at the time of EBT measurement.

Lastly, but very importantly, we identified two children with problem wheezing requiring anti-asthma therapy who had a very low EBT (19 and 27 °C), but excluded them from our analysis as they had primary ciliary dyskinesia (PCD). This is an important observation that may parallel that of the well-publicized findings of low ENO being detected in children with PCD.²⁴ Nasal nitric oxide measurement is now recommended as a screening test for PCD. It will require EBT to be studied in a much larger group of people with PCD to find out whether EBT could function as a cheap, easy-to-use screening test for this difficult-to-confirm disease. In addition, Carraro et al. have shown that EBT is low in a group of children with bronchopulmonary dysplasia (BPD) and hypothesized that this was resultant on the remodeled and reduced airway wall vasculature.²⁵ Other potential mechanisms

that could explain the low EBT in children with PCD or immune deficiencies could relate to the thicker blanket of bronchial mucus blocking the transfer of heat energy from the bronchial blood vessels to the air.

CONCLUSIONS

At a general secondary and tertiary pediatric respiratory clinic, we have observed that measurement of EBT is feasible in children as young as 5 years. The EBT level was not related to the physician's decision to alter treatment, the assessment of current asthma control, current BTS-step of therapy, lung function, or ENO. Routine measurement of EBT at the clinic can not be recommended. From the literature, EBT measurements may be the most useful when measured on a day-to-day basis by individual patients.

REFERENCES

1. British Thoracic Society/Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline. *Thorax* 2008;63:1–121.
2. Stevenson EC, Turner G, Heaney LG, Taylor R, Shields MD, Ennis M. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997;27:1027–1035.
3. Lex C, Ferreira F, Zacharasiewicz A, Nicholson AG, Haslam PL, Wilson NM, Hansel TT, Payne DN, Bush A. Airway eosinophilia in children with severe asthma: predictive values of non-invasive tests. *Am J Respir Crit Care Med* 2006;174:1286–1291.
4. Warke TJ, Fitch PS, Brown V, Taylor RA, Lyons JDM, Ennis M, Shields MD. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax* 2002;57:383–387.
5. Warke TJ, Mairs V, Fitch PS, McGovern V, Ennis M, Shields MD. Exhaled nitric oxide in relation to the clinical features of childhood asthma. *J Asthma* 2004;41:751–757.
6. de Jongste JC, Carraro S, Hop WC, CHARISM Study Group, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009;179:93–97.
7. Pike K, Selby A, Price S, Warner J, Connett G, Legg J, Lucas JS, Peters S, Buckley H, Magier K, et al. Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial. *Clin Respir J* 2013;7:204–213.
8. Paredi P, Kharitonov SA, Barnes PJ. Faster rise of EBT in asthma: a novel marker of airway inflammation? *Am J Respir Crit Care Med* 2002;165:181–184.
9. Piacentini GL, Bodini A, Zerman L, Costella S, Zanolla L, Peroni DG, Boner AL. Relationship between exhaled air temperature and exhaled nitric oxide in childhood asthma. *Eur Respir J* 2002;20:108–111.
10. Paredi P, Kharitonov SA, Barnes PJ. Correlation of exhaled breath temperature with bronchial blood flow in asthma. *Respir Res* 2005;6:1–10.
11. Piacentini GL, Peroni D, Crestani E, Zardini F, Bodini A, Costella S, Boner AL. Exhaled air temperature in asthma: methods and relationship with markers of disease. *Clin Exp Allergy* 2007;37:415–419.
12. Pifferi M, Ragazzo V, Previti A, Pioggia G, Ferro M, Macchia P, Piacentini GL, Boner AL. Exhaled air temperature in asthmatic children: a mathematical evaluation. *Pediatr Allergy Immunol* 2009;20:164–171.

13. Popov TA, Dunev S, Kralimarkova TZ, Kraeva S, DuBuske LM. Evaluation of a simple, potentially individual device for exhaled breath temperature measurement. *Respir Med* 2007;101:2044–2050.
14. Xepapadaki P, Xatzioannou A, Chatzicharalambous M, Makrinioti H, Papadopoulos NG. Exhaled breath temperature increases during mild exacerbations in children with virus-induced asthma. *Int Arch Allergy Immunol* 2010;153:70–74.
15. Peroni DG, Chinellato I, Piazza M, Zardini F, Bodini A, Olivieri F, Boner AL, Piacentini GL. Exhaled breath temperature and exercise-induced bronchoconstriction in asthmatic children. *Pediatr Pulmonol* 2012;47:240–244.
16. Robins S, Roussel L, Schachter A, Risse PA, Mogas AK, Olivenstein R, Martin JG, Hamid Q, Rousseau S. Steroid-insensitive ERK1/2 activity drives CXCL8 synthesis and neutrophilia by airway smooth muscle. *Am J Respir Cell Mol Biol* 2011;45:984–990.
17. Kralimarkova T, DuBuske L, Dimitrov V, Popov T. Exhaled breath temperature is influenced by both age and diagnosis of respiratory disease in children. *Allergy* 2011;66:575.
18. Logie KM, Kusel MMH, Sly PD, Hall GL. Exhaled breath temperature in healthy children is influenced by room temperature and lung volume. *Ped Pulmonol* 2011;46:1062–1068.
19. Kapande KM, McConaghy LA, Douglas I, McKenna S, Hughes JL, McCance DR, Ennis M, Shields MD. Comparative repeatability of two handheld fractional exhaled nitric oxide monitors. *Pediatr Pulmonol* 2012;47:546–550.
20. Garcia G, Granero N, Hendridriksen B, Carlos D, Ezequiel B, Bergna M. Exhaled breath temperature in adult cystic fibrosis. *Eur Resp Journal* 2011;38:4290.
21. Popov TA, Kralimarkova TZ, Lazarova CT, Tzachev CT, Dimitrov VD, Gill J. Daily monitoring of asthmatics by means of individual devices for exhaled breath temperature measurement. *IEEE Sens J* 2010;10:44–47.
22. Svensson H, Nilsson D, Bjermer L, Tufvesson E. Exhaled breath temperature increases after exercise in asthmatics and controls. *Respiration* 2012;84:283–290.
23. Peroni DG, Chinellato I, Piazza M, Zardine F, Bodini A, Olivieri F, Boner A, Piacentini GL. Exhaled breath temperature and exercise-induced bronchoconstriction in asthmatic children. *Ped Pulmonol* 2012;47:240–244.
24. Strippoli MP, Frischer T, Barbato A, Snijders D, Maurer E, Lucas JS, Eber E, Karadag B, Pohunek P, Zivkovic Z, et al. Management of primary ciliary dyskinesia in European children: recommendations and clinical practice. *Eur Respir J* 2012;39:1482–1491.
25. Carraro S, Piacentini G, Lusiani M, Uyan ZS, Filippone M, Schiavon M, Boner A, Baraldi E. Exhaled air temperature in children with bronchopulmonary dysplasia. *Ped Pulmonol* 2010;45:1240–1245.