

Exhaled Breath Temperature Increases during Mild Exacerbations in Children with Virus-Induced Asthma

P. Xepapadaki A. Xatzioannou M. Chatzicharalambous H. Makrinioti
N.G. Papadopoulos

Allergy Department, Second Pediatric Clinic, University of Athens, Athens, Greece

Key Words

Airway inflammation • Asthma, virus-induced • Asthma, child • Exhaled breath temperature

Abstract

Background: Exhaled breath temperature (EBT) has been suggested as a non-invasive surrogate marker of airway inflammation in asthma. The aim of the study was to evaluate differences in EBT between periods of controlled disease and during exacerbations in children with virus-induced asthma. **Methods:** Twenty-nine children (aged 6–14 years) with a history of intermittent, virus-induced asthma were included in this case-control study. Cases presented with a common cold and/or mild exacerbation of asthma, while controls were free of asthmatic or common cold symptoms during the previous 6 weeks. A baseline questionnaire was obtained. Atopy assessment, central temperature and a spirometric measurement were recorded. EBT was measured with a new device (Delmedica, Singapore). A nasal wash (for identification of common respiratory viruses) was obtained. **Results:** Twenty-four children (12 from each group) completed the study. Groups were homogeneous with respect to baseline characteristics. PCR revealed the presence of a virus in 3 out of 17 controls and 10 out of 12 cases (17.6 and 83.3%,

respectively, $p = 0.002$). The most commonly identified virus was rhinovirus (3/3 controls and 7/10 cases, $p = 0.02$). EBT values were significantly higher for cases ($34.91 \pm 0.62^\circ\text{C}$) compared to controls ($34.18 \pm 1.1^\circ\text{C}$, $p = 0.032$). No important differences were observed in the increase rate of EBT ($\Delta e^\circ\text{T}$) between groups. **Conclusions:** Changes in airway inflammation during virus-induced asthma exacerbations are reflected in EBT changes. These preliminary data suggest a possible role of EBT measurements in the assessment of airway inflammation in children with virus-induced asthma.

Copyright © 2010 S. Karger AG, Basel

Introduction

Asthma is a chronic inflammatory disease [1]. Inflammation, by definition, is characterized by – among others – increased production of heat. Histological examination of the asthmatic airway wall has revealed increased vascularity, while soluble inert gas uptake methods have demonstrated increased bronchial blood flow in asthmatics. Such changes probably contribute to the regulation of airway temperature, as indicated by the finding that temperature changes are able to induce bronchoconstriction [2, 3]. It is therefore reasonable to hypothesize

that exhaled breath temperature (EBT) may reflect heat in the asthmatic airways and therefore may serve as a marker of airway inflammation.

It has been shown that asthmatics present faster increases of EBT during a single breath inhalation compared to normal controls [4]. EBT has also been positively correlated with concentrations of exhaled nitric oxide (NO), a well established marker of inflammation [5]. Similar findings have been reported in children, where positive associations have been demonstrated between peak and plateau EBT values and NO [6]. More recently, bronchial blood flow has been significantly correlated with the rate of EBT increase and NO values in asthmatics [7], while thermal measurements have also been associated with eosinophilic inflammation in asthmatic adults and children [8, 9].

Although the above data suggest significant differences in EBT between asthmatic and normal individuals, there is no available information on possible EBT changes over time, particularly during exacerbations of the disease. Such differences, if present, could also suggest that EBT measurements could be explored in asthma monitoring.

The overwhelming majority of acute asthma exacerbations are viral in origin [10, 11]. We hypothesized that changes in inflammatory activity during mild exacerbations can be reflected in changes in EBT. The aim of the present study was to evaluate differences in EBT between periods of controlled disease and during exacerbations in children with virus-induced asthma.

Materials and Methods

Patients

Twenty-nine children (aged 6–14 years) were included in this cross-sectional, case-control study. Inclusion criteria were asthma diagnosis according to international guidelines (GINA, PRACTALL), classification as intermittent according to GINA 2006 and virus-induced phenotype according to PRACTALL [1], although overlaps between phenotypes as suggested in the aforementioned guidelines could not be excluded. Children had to be able to perform spirometric maneuvers. Control children were recruited among asthma patients followed up in our outpatient clinic and presenting for a scheduled visit at which they reported no symptoms of asthma, rhinitis or a common cold during the last 6 weeks. Cases were children presenting with mild respiratory symptoms such as mild cough or wheezing on occasions (suggestive of mild lower respiratory tract involvement or mild asthma exacerbation) and not having received anti-inflammatory treatment for the current episode. None of the children received nasal corticosteroids, antihistamines or leukotriene receptor antagonists. Subjects were excluded from the study if they suffered from

any other acute disease or other chronic respiratory diseases (e.g. cystic fibrosis, bronchopulmonary dysplasia, primary ciliary dyskinesia syndrome). Severe asthma exacerbations were also excluded both because of possible treatment interference and due to difficulty in performing the EBT measurement.

Participants completed a baseline questionnaire that included demographic characteristics and information on duration and severity of asthma during the last year, the number of viral infections and presence of other atopic diseases. After a full clinical examination, EBT was measured with a prototype device (Delmedica, Singapore) as described by Popov et al. [12]. Reproducibility of the device's measurements has been shown to be relatively high. In detail, subjects were instructed to hold the device with their two hands, purse their lips around the mouthpiece and to exhale freely into the device at a rate and depth suiting their normal tidal breathing pattern, as if inflating a balloon. Inhalation was performed through the nose. Thermal indications were recorded at 1 min intervals until the same value was repeated on 2 consecutive measurements 1 min apart. The estimated time for reaching thermal equilibrium was 5–10 min. Children did not receive any short-acting bronchodilators at least 8 h prior to lung function testing. The test was carried out at a room temperature of 19–25°C, and a relative humidity of 30–60%. We performed atopic sensitization by means of skin prick tests (SPT) to a panel of locally relevant allergens, central temperature (otic) and a spirometric measurement after EBT recordings using a Jaeger spirometer.

Viral Identification

A nasal wash was obtained and reverse transcription-PCR (RT-PCR) was used for detection of viral RNA in nasal washing samples as previously described [13, 14]. PCR reactions were performed for rhinoviruses, adenoviruses, respiratory syncytial virus, metapneumovirus, coronaviruses, influenza viruses A and B, parainfluenza viruses 1, 2 and 3, and bocavirus [15].

The study was approved by the ethical committee of P-A Kyriakou Children's Hospital. Parents were informed about the purpose and methods of the study and gave written consent.

Statistical Analysis

SPSS version 13 was used for the statistical analysis. The temperature data were normally distributed (Kolmogorov-Smirnov test) and were compared by an independent sample *t* test. Comparisons of descriptive characteristics between the 2 groups were made by χ^2 . Correlations were determined using a Pearson correlation coefficient. Data were expressed as means $\pm$ SD. Significance was defined as $p < 0.05$.

Results

Baseline Characteristics

Twenty-four children (12 from each group) completed the study. Five children from the baseline failed to accomplish a reliable EBT measurement. These children did not differ in any of the characteristics examined from those who completed the study (not shown). Table 1

Table 1. Descriptive characteristics of asthmatic children without respiratory symptoms (controls) and asthmatic children with a mild exacerbation (cases)

Descriptive characteristics	Controls (n = 12)	Cases (n = 12)
Age, years	9.6 ± 2.3	8.8 ± 1.8
Boys, %	58.8	75
SPT positive, %	76	90
Exposed to tobacco smoke, %	60	41.6
Education level		
Father completed secondary education, %	58.3	33.3
Mother completed secondary education, %	50	50
Asthma exacerbations in the previous year, n	1.7 ± 0.49	1.25 ± 1.05
Body temperature, °C	36.71 ± 0.31	36.73 ± 0.32
FEV ₁ , % predicted	99.6 ± 9.8	93.08 ± 16.1
Change in FEV ₁ after bronchodilation, l	1.45 ± 6.8	5.6 ± 6.1
FEF _{25–75} , % predicted	98.6 ± 24.2	91.9 ± 33.9
Change in FEF _{25–75} after bronchodilation, l/s	10.7 ± 19.0	19.1 ± 20.2

No p values were significant. Values are mean ± SD unless indicated otherwise.

shows the demographic, socioeconomic and disease characteristics, which were homogeneous between groups for included children. Baseline spirometric values showed no significant differences when statistically compared between groups; however, in cases we noted a trend towards presenting lower FEV₁ baseline values and increased FEF_{25–75} changes after bronchodilation than controls (table 1).

Detection of Respiratory Viruses

A respiratory virus was present in 3 of 17 controls and 10 of 12 cases (17.6 and 83.3%, respectively, $p = 0.002$). The most commonly identified virus was rhinovirus (3/3 controls and 7/10 cases, $p = 0.02$). Three cases were positive for influenza (0 of 17 controls, 3 of 12 cases, $p = 0.03$). One control was positive for adenovirus, 1 control and 1 case for parainfluenza. All specimens were negative for the presence of MPV, corona or boca viruses.

EBT Determination

EBT values were almost 1°C higher in symptomatic children (EBT = 34.91°C ± 0.62), compared to asthmatic children without current or recent respiratory symptoms (EBT = 34.09°C ± 0.95, $p = 0.02$; fig. 1). The mean time to reach thermal equilibrium did not differ between the 2 groups (controls 7.5 ± 2.9 min, cases 8.08 ± 1.7 min, $p = 0.5$). Symptomatic children had a marginally higher exhaled temperature increase rate ($\Delta e^{\circ}T$) [4] in comparison to the controls (0.14 ± 0.09°C/min vs. 0.07 ± 0.06°C/min, respectively, $p = 0.06$).

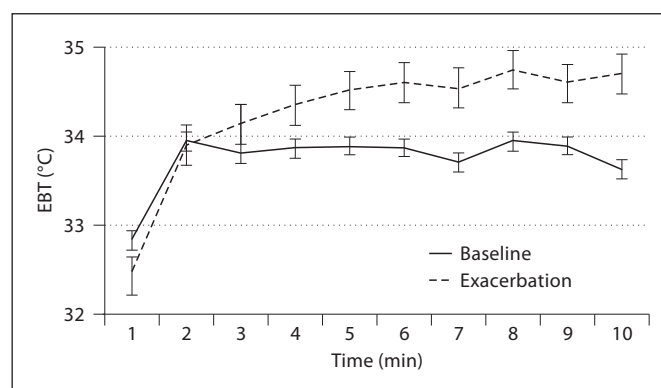


Fig. 1. Mean EBT values (± SE) in children with virus-induced asthma at baseline and during a mild exacerbation, during 10 continuous measurements (per minute).

No significant correlations were observed between EBT and spirometric indices including FEV₁ ($p = 0.1$) or FEV₁% predicted ($p = 0.8$) and FEF₅₀ ($p = 0.7$) or FEF₅₀% predicted ($p = 0.6$).

Discussion

This proof-of-concept study is the first to show that children with a mild exacerbation of virus-induced asthma have higher EBT values than non-symptomatic asthmatic children of the same phenotype. EBT values (°C)

in our study are similar to those published previously, although these studies have mainly dwelt upon the EBT differences between asthmatics and controls. Popov et al. [12], using the same device, reported significant differences in EBT plateau values between asthmatic (median 35.45°C, range 34.12–36.09°C) and control adults (median 34.84°C, range 32.29–35.84°C). Paredi et al. [4], using a different technique, did not find significant differences in end-expiratory plateau temperature between asthmatic and normal adults (35.75 ± 0.6°C and 34.45 ± 0.8°C); however, measurements in asthmatic children by Piacentini et al. [6] were slightly lower than the aforementioned (peak expiratory temperature: 32.4 ± 0.2°C). Differences in the device used may account for this discrepancy.

It is well established that almost 60–70% of asthmatic children with a virus-induced phenotype will develop an exacerbation after a viral infection [10, 16]. The increase of EBT values recorded in this study was at an early stage and/or during a mild exacerbation, when no major systemic effects were observed: no change in central temperature and a very mild (~6%), non-significant drop in FEV₁. These findings suggest that EBT may prove sensitive enough to monitor the activity of virus-induced asthma.

Previous studies in animal models and humans have proved that asthma is associated with increased airway blood flow, either due to new vessel formation, vasodilatation or inflammation [2]. Changes in bronchial circulation can alter air stream temperature, by means of EBT values and are also correlated with airway inflammation as assessed by exhaled nitric oxide (eNO) [7]. Moreover, eNO levels are elevated at the onset of exacerbation, particularly in the presence of a cold, while the same has been reported for EBT measurements [12, 17, 18]. On the other hand, rhinoviral respiratory infections have been shown to promote angiogenesis through the induction of angiogenic factors such as vascular endothelial growth factor (VEGF), thus contributing to airway remodeling [19]. Whether the increased EBT measurements are due to viral infection per se or the subsequent asthma exacerbation cannot be conclusively inferred by the current study design. Taking into account that more than 85% of exacerbations are associated with a viral infection and that the exacerbation usually occurs 1–2 days after the symptomatic presentation of the cold, daily measurements in a large cohort may be required for such a differentiation. A longitudinal study is underway and is assessing several markers of lung function and airway inflammation in order to determine in a more comprehensive way the predictive role of EBT in respect to an exacerbation.

Previous investigators have shown that adult patients with asthma have elevated rates of EBT increase ($\Delta e^{\circ}T$) compared to normal subjects [4]. In our study, elevated rates in EBT increase were noted in symptomatic asthmatic children; however, this difference was not statistically significant, probably due to the device used or the small number of children included. Popov et al. [12] showed that the time to reach thermal equilibrium did not differ between asthmatics and normal adult controls, probably due to the dependency of the specific device on individuals' patterns of respiratory maneuver [12].

EBT in our study did not correlate with spirometric indices, similarly to previous reports [9]. Children in our study reported mild exacerbations, reflected by the nearly normal spirometric indices. It has been repeatedly shown that lung function, inflammation and symptoms vary independently in asthma [20].

Most of the children performed the maneuvers for EBT successfully, although the time to complete a measurement was more than had been anticipated. This was possibly because the device used was a prototype. A smaller version is currently being marketed (X-halo, Delmedica).

In conclusion, the results of this small, proof-of-concept study indicate that changes in airway inflammation during virus-induced acute asthma exacerbations are reflected in EBT changes. These preliminary data suggest a possible role of EBT increases as markers of airway inflammation in children with a virus-induced asthma phenotype. A longitudinal study assessing the predictive potential of EBT in virus-induced asthma is currently underway.

References

- 1 Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills T, Pohunek P, Simons FE, Valovirta E, Wahn U, Wildhaber J: Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;63:5–34.
- 2 Kumar SD, Emery MJ, Atkins ND, Danta I, Wanner A: Airway mucosal blood flow in bronchial asthma. *Am J Respir Crit Care Med* 1998;158:153–156.
- 3 McDonald DM: Angiogenesis and remodeling of airway vasculature in chronic inflammation. *Am J Respir Crit Care Med* 2001;164:S39–S45.
- 4 Paredi P, Kharitonov SA, Barnes PJ: Faster rise of exhaled breath temperature in asthma: a novel marker of airway inflammation? *Am J Respir Crit Care Med* 2002;165:181–184.

- 5 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.
- 6 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.
- 7 Paredi P, Kharitonov SA, Barnes PJ: Correlation of exhaled breath temperature with bronchial blood flow in asthma. *Respir Res* 2005;6:15.
- 8 Piacentini GL, Bodini A, Peroni D, Ress M, Costella S, Boner AL: Exhaled air temperature and eosinophil airway inflammation in allergic asthmatic children. *J Allergy Clin Immunol* 2004;114:202–204.
- 9 Noble DD, McCafferty JB, Greening AP, Innes JA: Respiratory heat and moisture loss is associated with eosinophilic inflammation in asthma. *Eur Respir J* 2007;29:676–681.
- 10 Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DAJ, Holgate ST: Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995;310:1225–1228.
- 11 Xepapadaki P, Papadopoulos NG: Viral infections and allergies. *Immunobiology* 2007;212:453–459.
- 12 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.
- 13 Papadopoulos NG, Hunter J, Sanderson G, Meyer J, Johnston SL: Rhinovirus identification by Bgl I digestion of picornavirus RT-PCR amplicons. *J Virol Methods* 1999;80:179–185.
- 14 Spyridaki IS, Christodoulou I, de Beer L, Hovland V, Kurowski M, Olszewska-Ziaber A, Carlsen KH, Lodrup-Carlsen K, van Drunen CM, Kowalski ML, Molenkamp R, Papadopoulos NG: Comparison of four nasal sampling methods for the detection of viral pathogens by RT-PCR-A GA(2)LEN project. *J Virol Methods* 2009;156:102–106.
- 15 Papadopoulos NG, Moustaki M, Tsolia M, Bossios A, Astra E, Prezerakou A, Gourgiotis D, Kafetzis D: Association of rhinovirus infection with increased disease severity in acute bronchiolitis. *Am J Respir Crit Care Med* 2002;165:1285–1289.
- 16 Bardin PG, Johnston SL, Pattemore PK: Viruses as precipitants of asthma symptoms. II. Physiology and mechanisms. *Clin Exp Allergy* 1993;22:809–822.
- 17 Bhowmik A, Seemungal TA, Donaldson GC, Wedzicha JA: Effects of exacerbations and seasonality on exhaled nitric oxide in COPD. *Eur Respir J* 2005;26:1009–1015.
- 18 Murphy AW, Platts-Mills TA, Lobo M, Hayden F: Respiratory nitric oxide levels in experimental human influenza. *Chest* 1998;114:452–456.
- 19 Psarras S, Volonaki E, Skevaki CL, Xatzipsalti M, Bossios A, Pratsinis H, Tsigkos S, Gourgiotis D, Constantopoulos AG, Papapetropoulos A, Saxoni-Papageorgiou P, Papadopoulos NG: Vascular endothelial growth factor-mediated induction of angiogenesis by human rhinoviruses. *J Allergy Clin Immunol* 2006;117:291–297.
- 20 van Den Toorn LM, Prins JB, Overbeek SE, Hoogsteden HC, de Jongste JC: Adolescents in clinical remission of atopic asthma have elevated exhaled nitric oxide levels and bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2000;162:953–957.