MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 5(6) pp. xxx-xxx, June, 2017
Available online http://www.meritresearchjournals.org/mms/index.htm


*Original Research Article*

# Exhaled breath temperature in children with asthma, correlation with spirometry, blood eosinophils and exhaled nitric oxide

**Stoeva T[1]*, Tzocheva I[2], Mileva S[2], Yankowa M[2] and Galabova M[3]**

[1]Paediatric Pulmonologist at Pediatric respiratory center South park, Sofia, Bulgaria

[2]Paediatric Pulmonologists at Department of paediatrics, University hospital Alexandrovska, Sofia, Bulgaria

[3]Paediatric pulmonologist at Department of paediatrics, University hospital St. Marina, Varna, Bulgaria

***Corresponding Author E-mail: t.stoeva@hotmail.com**
**Phone number: 00359888393253**

**Abstract**

**Recently, several studies have documented high Exhaled Breath Temperature (EBT) in children and adults with asthma. EBT has been suggested as a promising non-invasive marker of airway inflammation. The aim of this study is to compare the EBT of asthmatic children versus healthy controls and to evaluate correlations with spirometry, blood eosinophils count and fraction of exhaled nitric oxide (FeNO). 102 patients were enrolled (62 Male 40 Female, aged 6-16 yrs) and 30 age matched controls. History, physical examination, EBT values (X-halo, Delmedica, Singapour), were evaluated followed by FeNO (NIOX MINO, Aerocrine, Sweden), pulmonary function tests and blood sample for eosinophils count. The mean EBT was greater in asthmatics compared to controls (32.29°C vs 30.92°C, p=0.005). In the asthmatic group there were positive correlation between EBT and FENO (r=0.456; p<0.001) as well between EBT and blood eosinophils count (r=0.407; p<0.001) and negative with FEV1%pred (r=(-)0.36, p<0.001). Conclusions: There is a significant difference in mean EBT values between asthmatic and healthy children. We found positive correlation between EBT, FeNO and blood eosinophils count, which suggest that EBT could also serve as marker for airway inflammation in children with asthma.**

**Key words:** Asthma, Children, Exhaled breath temperature, Exhaled nitric oxide

## INTRODUCTION

Asthma is characterized by chronic inflammatory process in the airways. The need to monitor airway inflammation in asthma, particularly in paediatric populations, has led to the development of a number of non-invasive methods of assessment, including analysis of cells and cell products in sputum samples collected by means of induced sputum, as well as the measurement of exhaled markers and soluble mediators obtained from exhaled breath condensates. (Gibson, 2000) FeNO is the best studied nonivasive inflammatory marker proven to reflect eosinophilic airway inflammation in asthma (Dweik 2011). Recently several studies have described high exhaled breath temperature (EBT) in asthmatic subjects. (Paredi 2002; Piacentini 2007)

The concept of introducing EBT as a surrogate marker of inflammation rises from the assumption that airway inflammation in asthma is accompanied by production of heat. Histological examination of the asthmatic airway wall has revealed increased vascularity (Carroll 1997; Kumar 1998) and increased bronchial blood flow. Such changes probably contribute to the regulation of airway temperature, as indicated by the finding that temperature changes are able to induce bronchoconstriction (Gilbert, 1992). Several studies have shown that EBT is closely related to underlying inflammation in asthma (Paredi 2002, 2005). Many inflammatory mediators known to be released in asthma may contribute to bronchial vascular dilation and thus to EBT. These include histamine,

bradykinin, leukotrienes, prostaglandin $E_2$, adenosine (Brodmann, 2001) and nitric oxide (NO). NO plays an important role in regulating bronchial vascular tone and increasing bronchial blood flow (Degnim, 1996). Since patients with asthma have higher concentrations of exhaled NO compared with normal subjects it could be suggested that their breath temperatures will be also higher. To date many studies documented utility , reproducibility and relations with disease activity of EBT in adults (Paredi, 2005, Piacentini, 2007; Melo, 2010) but those related to paediatric subjects with asthma are only few. (Piacentini, 2002; Leonardi, 2015) The objective of this study is to compare the EBT of asthmatic children and healthy controls, and to evaluate correlations with spirometry, blood eosinophils count and fraction of exhaled nitric oxide (FeNO).

## METHODS

### Subjects

One hundred and two caucasian children were recruited (62 males and 40 females; aged between 6 and 16 years) who were referred to the Pediatric Department, University hospital Lozenetz, Sofia, Bulgaria between January 2013 and January 2015. Sixty nine subjects were admitted for suspected asthma on the basis of clinical history of repeated episodes of coughing, dyspnea, wheezing and short acting $\beta$2-agonist administration. The diagnosis asthma was made by an experienced paediatric respiratory physician according to GINA criteria (GINA 2015). For the rest 33 of the asthmatics the diagnosis have been already established and they were referred to the clinic for routine asthma visit. All asthmatic children were separated in two groups as follows: those with recently diagnosed asthma, controller naive and those with previously diagnosed asthma on controller medication treatment. Thirty age matched healthy children (18 males and 12 females) without previous history for lower respiratory illness, wheeze or allergic disorders (food allergy, eczema, hay fever) or parental asthma were recruited from those attending for routine immunisation. The study was approved by the Ethical Committee of the hospital. Written informed consent was obtained from all parents.

### Exhaled Breath Temperature (EBT)

Exhaled breath temperature was measured during tidal breathing with on-line breath thermometer (X halo, Delmedica, Singapore), after measurement of axilliary temperature, and in room environment temperature no higher than 21ºC. The exhalation continued until a temperature plateau for at least 3 seconds.

### Fraction of exhaled nitric oxide (FeNO)

FeNO was determined with an on-line method using a single breath exhalation with electrochemical device (NIOX MINO; Aerocrine AB; Solna, Sweden), according to ATS-ERS standarts (1). Patients made an inspiration of eNO-free air via a mouthpiece immediately followed by full exhalation at a constant rate (50mL/sec) for at least 5 seconds. 15 ppb or more were considered elevated values, according to ATS-ERS criteria (1)

### Pulmonary Function Test (PFT)

PFT was determined by spirometry with a calibrated computerized spirometer (Micromedical, Rochester, UK). Standard measures of pulmonary function were collected, including FVC, FEV1, and MEF at 50%, 25%, 75%, 25-75% of VC. All tests were performed according to the current ATS/ERS spirometry standards (25). The baseline indices was selected using the best-of-three results based on the highest sum of FVC and FEV1%pred.

### Inflammatory Cells

Percentage of peripheral blood eosinophils counts were measured in capillary blood sample by automatic haematological analyzer on the basis of cytological determination.

### Statistical Analysis

Statistical analyses and data presentation were performed with the SPSS computer software package (version 11.0; SPSS, Chicago, IL, USA) The comparison of each parameter among normal distribution was performed with the Student's t-test otherwise with Mann-Whitney test and by unpaired T-test. Correlations among parameters were made by using the Pearson or Spearman correlation coefficient. The comparison of the differences between the two groups was calculated also using the Chi square ($\chi$2) and AVONA. Test Statistical significance level was $P < .05$.

## RESULTS

The results of in 102 asthmatic children (mean age 7.8 years) and 30 aged matched controls (mean age 8.1 years) were analysed. The asthmatic subjects were separated in two groups: controller naive asthmatic children with recently diagnosed asthma (n=69) and children with previously diagnosed asthma (n=33) treated with controller medications. During the investigation

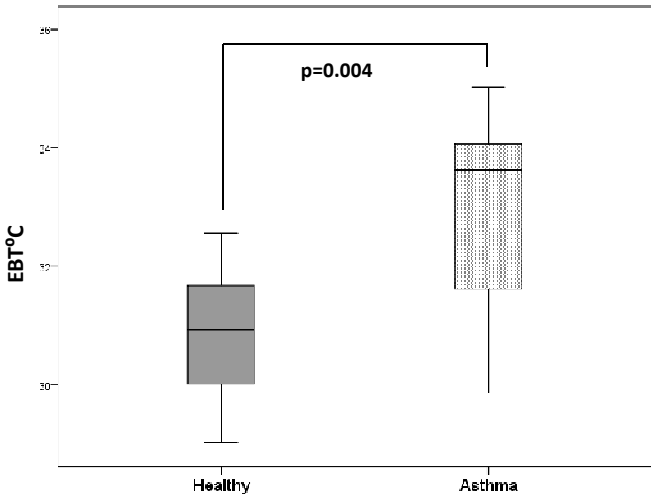


**Figure 1.** Mean EBT°C values in healthy children and asthmatics

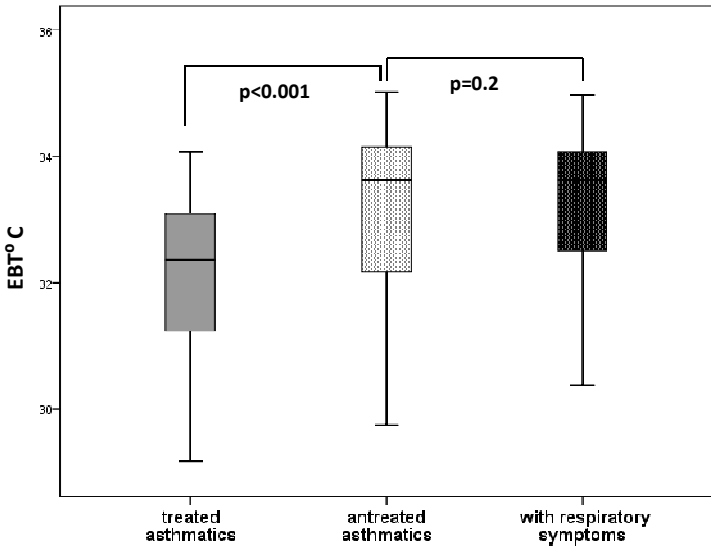


**Figure 2.** Difference in mean EBT°C values in children with asthma

44.1% (n=45) of the asthmatics showed acute respiratory symptoms. Positive family history for asthma and allergies were found in 47 of the children, more frequently in group of asthmatics with previously diagnosed asthma (p=0.001). Thirty three of asthmatics had accompanying allergic rhinitis (AR). The distribution of EBT in both asthma groups and in healthy children differs from normal (Kolmogorov-Smirnov test, p=0.004). There was significant difference in EBT values between asthmatic and control group (32.56ºC; SD 1,6 vs. 30.92ºC; SD 1.00 (p=0.004) and EBT values in asthmatics were higher than in controls (Figure 1).

The average body temperature was similar in both groups (36.23℃ vs 32.38 ℃, p> 0.05). We did not find any difference in EBT values between males and females in groups of asthmatics and controls (p=0.7 and p=0.3). Positive correlation was found between EBT and age of the investigated children and we established that EBT increases with age (r=0.338, p<0.001), while reported family history did not affect EBT (p=0.2). In asthmatic children with concomitant AR the values EBT were higher than in those who had only asthma (EBT 33.14 ºC vs. 32.29ºC p=0.01). FeNO measurement showed similar findings and were higher in asthmatics compared to controls with further elevation in children with asthma and AR (42.21 vs.23.07, p<0.001). EBT was higher in controller naïve children compared to treated asthmatics (33.03ºC vs. 32.67ºC, p<0.001) (Figure 2). There was a

**Table 1.** Correlation between EBTºC and FeNOppb in investigated children

| Correlation between EBT ºC and FeNO ppb | Spearman's correlation coefficient | p value |
|---|---|---|
| Children with asthma (n=102) | 0.46 | p<0.001 |
| Recently diagnosed asthma (controller naive) (n=69) | 0.69 | p<0.001 |
| Previously diagnosed asthma ( on controller treatment) (n=33) | 0.44 | p=0.2 |
| Asthmatics with acute respiratory symptoms (n=45) | 0.62 | p<0.001 |
| Healthy children (n=30) | 0.38 | p=0.3 |

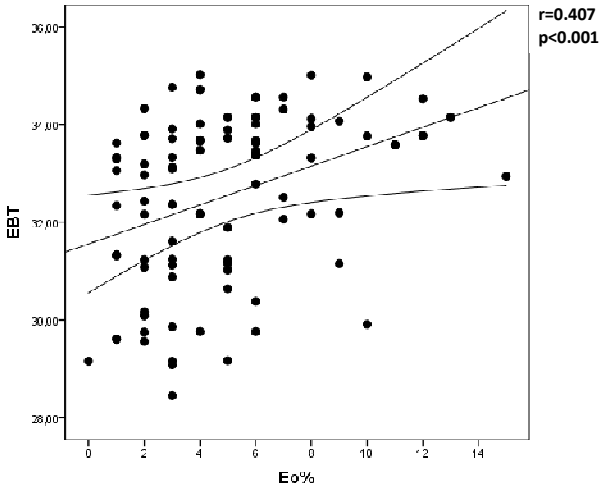


**Figure 3.** Correlation between EBTºC and percentage of blood eosinophils count (Eo%) in asthmatic subjects

tendency towards elevation of EBT in children with acute respiratory symptoms (mean EBT-33.18ºC) during investigations, although not statistically significant (p=0.2).

The mean FeNO values showed similar statistical changes within both groups of asthmatics and were lower in asthmatics on controller therapy compared to untreated (36.29 ppb vs. 23.79, p=0.003). There was positive correlation between FeNO and EBT in controller naïve asthmatics with newly diagnosed asthma (r=0.456, p <0.001) and in those with acute bronchial obstruction in both asthma groups (r=0.623, p<0.001). In contrast the correlation between FeNO and EBT for the rest of the children was insignificant (Table 1).

In children with asthma both EBT and FeNO were positively correlated with percentage of peripheral blood eosinophils count (Figure 3 and Table 2).

A weak but statistically significant negative relation was found between EBT, FeNO and the indices of the pulmonary function test by means of FEV1%pred (EBT , r = (-) 0.36, p<0.001; FeNO , r = (-) 0.255,p=0.01 ) and fall of FEV1 % pred was associated with elevations of the values of both EBT and FeNO. At the same time FEV1%pred levels did not differ significantly between both groups of asthmatics, although were lower compared to controls (85.49%pred vs. 93.50%pred, p<0.001).

Children with previously diagnosed asthma (n=33) were separated by their asthma controller treatment regimes as follows: LTRA (n=20); ICS (n=7); ICS/LTRA (n=3); ICS/LABA (n=3) .We found that asthmatics treated with combination therapy ICS/LABA have the lowest EBT values (AVONA, p=0.01) while ICS alone caused greater reduction in FeNO. (AVONA, p=0.01). (Figure 4)

**Table 2.** Correlations between EBT, FeNO, FEV1%pred, Eo% in asthmatics and healthy subjects

| Asthmatics Whole group | **Spearman's correlation coefficient** | p | Healthy | **Spearman's correlation coefficient** | p |
|---|---|---|---|---|---|
| EBT°C /FEV1%pred | (-) 0.36 | <0.001 | EBT°C /FEV1%pred | 0.123 | 0.5 |
| EBT°C/Eo% | 0.456 | <0.001 | EBT°C/Eo% | (-)0.43 | 0.2 |
| FeNOppb /Eo% | 0.452 | <0.001 | FeNOppb /Eo% | 0.461 | <0.001 |
| FeNOppb /FEV1%pred | (-)0.255 | 0.01 | FeNOppb /FEV1%pred | (-)0.104 | 0.5 |

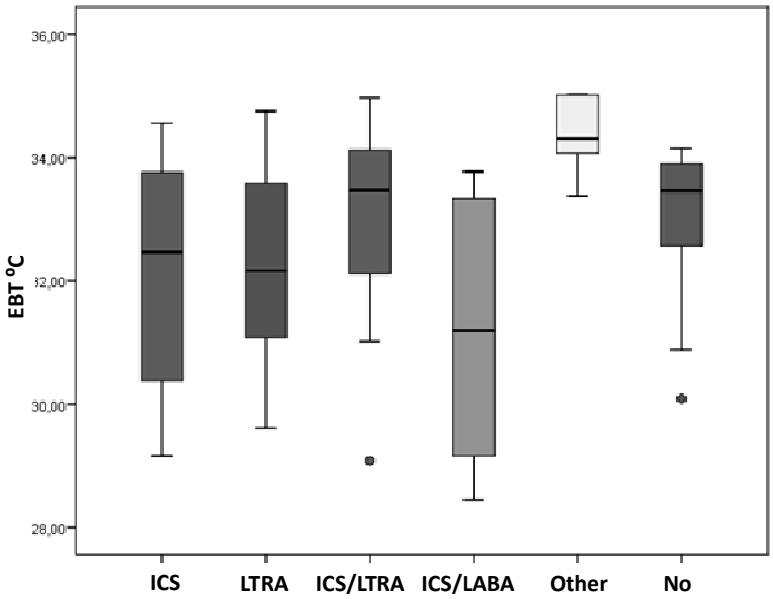


**Figure 4.** Difference of EBT°C values according to treatment* options in treated asthmatics
*ICS-inhaled corticosteroids, LTRA- leucotriene antagonists, LABA – long acting agonists

## DISCUSSION

Recently several studies have shown increased EBT in asthmatic subjects. It has been suggested that airway inflammation and a high concentration of NO may cause vasodilation of the bronchial circulation, contributing to increased heat exchange in airways of asthmatics. NO is a gas produced by several types of pulmonary cells, including inflammatory, endothelial, and airway epithelial cells. Elevated levels of exhaled NO in asthma (Robbins, 1994) are due to the activation of iNOS the inducible enzyme form responsible for the synthesis of NO. (Forstermann, 1991). As noticed previously exhaled NO reflects eoshinophilic airway inflammation and thus can predict corticosteroid responsiveness. In addition, the activity of iNOS, is temperature-dependent (Venturini, 1999), therefore elevated airway temperature in patients with asthma may induce further synthesis of NO. NO plays a major role in the regulation of bronchial blood flow (Fagan, 1999). Elevated levels of NO lead to vasodilation, increased bronchial blood flow, and exhaled breath temperature. The present study shows that children with asthma have greater exhaled breath temperature compared to healthy subjects and that it correlates to degree of airway inflammation measured by means of exhaled NO in untreated asthmatics and in asthmatic children with acute respiratory symptoms. These findings are in agreement with previously reported

relation between FeNO and EBT. (Piacentini, 2002) EBT levels were higher in asthmatics with accompanying AR compared to those who had only asthma. These results are similar to previously described greater increase in FeNO in subjects with asthma and AR compared to those with only asthma. (Kharitonov, 1997; Kimberly, 1996)

Since data in this study show strong relation between FeNO and EBT one can suggest that EBT will increase further when both upper and lower airways are involved in inflammatory process. There was not significant correlation between both parameters in treated asthmatics. As noticed previously, controller asthma medication due to their strong anti-inflammatory potential cause reduction in FeNO levels and ICS make this reduction to greatest extent (Jones, 2002). Ullien (Ullien, 1999) reported that ICS have also potential to reduce bronchial blood flow by enhancing activity of vasoconstrictor stimuli such norepinephrine and angiotensin II. In this study 33 children were treated with asthma controller medications. FeNO as well EBT values in this group of children were lower compared to untreated, steroid naive asthmatics. The combination therapy ICS /LABA cause fall in EBT values to greater extent compared with other treatment options. These findings are in agreement with previously reported data describing that adding LABA to ICS cause greater reduction in EBT than ICS only by diminishing capillary blood flow and thus liquid exudation from postcapillary venulae. (Caroll, 1997)

FeNO has been purposed as surrogate marker for eosinophilic airway inflammation and some studies have shown association between FeNO and peripheral blood eosinophils count. (Mattes, 1999) In this study we have found good correlation between FeNO and EBT and both correlated with blood eosinophils count therefore we can conclude that EBT like FeNO can also serve as surrogate marker for eosinophylic airway inflammation in non-invasive way. To date several studies have evaluated the relationship between EBT and parameters of lung function tests but their results are referred to adults (Paredi, 2002). In the present study there was a weak but significant negative correlation between exhaled breath temperature and FEV1%pred which shows that EBT increases when FEV1%pred falls. A reduction in airway caliber caused by increased vascularity and bronchial blood flow may explain the negative correlation between exhaled air temperature and FEV%pred. This hypothesis is supported by our findings since EBT shows tendency toward elevation in patients with acute respiratory symptoms although insignificantly. The data in our study are in agreement with previously reported findings by other researches. (Xepapadaki, 2010) Xepapadaki et al described that EBT increases during virally induced asthma exacerbations. Piacentini et al (Piacentini, 2002) reported increase in both FENO and EBT during exacerbations of treated asthmatics. Several other studies have described significant negative relation between FeNO and FEV1%pred. (Roslas,2004; Spergel, 2005) Given the fact that many asthma exacerbation are accompanied by fall of FEV1%pred we may suggest that in such cases rise of EBT could predict asthma worsening.

## CONCLUSION

Children with asthma have higher EBT values than healthy children. It's levels are higher in controller naive asthmatics and in those with asthma and accompanying AR. EBT decreases with asthma controller medications treatment. There are a positive correlation between FENO, blood eosinophils count and EBT and negative between EBT and spirometric indices. Since all these findings show many similarities with well known marker such FeNO we can suggest that EBT may also serve as objective non-invasive parameter for diagnosis and monitoring of eosinophylic airway inflammation in children with asthma. Further prospective studies on lager populations of children are required to confirm these conclusions.


## ACKNOWLEDGMENTS

It is my pleasure to submit current article as an original paper to your journal. The content of this paper has not been published or submitted for publication elsewhere and approved by all co-authors. All authors have contributed significantly and are in agreement with the content of the manuscript


## Conflict of Interest

The authors declare that they have no conflict of interest.

### REFERENCES


ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. Am J Respir Crit Care Med 2011;171:912-930

Brodmann M, Stelzer I, Friedl I, Lueger A, Pilger E, Stark G (2001). Comparison of the effect of prostaglandin E(1), prostacycline and adenosine on peripheral vascular resistance. Int J Angiol; 10: 31-33

Carroll NG, Cooke C, James AL (1997). Bronchial blood vessel dimensions in asthma. Am J Respir Crit Care Med; 155: 689-695

Degnim AC, Nakayama DK (1996). Nitric oxide and the pulmonary artery smooth muscle cell. Semin Pediatr Surg; 5: 160-164

Dweik RA, Boggs PB, Erzurum SC, et al., (Provide names of other authors) (2011). An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am. J. Respir. Crit. Care Med.; 184(5):602–615

Fagan KA, Tyler RC, Sato K, Fouty BW, Morris KGJ, Huang PL, McMurtry IF, Rodman DM (1999). Relative contributions of endothelial, inducible, and neuronal NOS to tone in the murine pulmonary circulation. Am J Physiol; 277: L472-L478

Forstermann U, Schmidt HH, Pollock JS, et al. (Provide names of other authors) (1991). Isoforms of nitric oxide synthase. Characterization and purification from different cell types. Biochem Pharmacol;42:1849-57

Gibson PG, Henry RL, Thomas P (2000). Noninvasive assessment of airway inflammation in children: induced sputum, exhaled nitric oxide, and breath condensate. Eur Respir J;16:1008-15.

Gilbert IA, McFadden ERJ (1992). Airway cooling and rewarming: the second reaction sequence in exercise induced asthma. J Clin Invest; 90: 699-704

GINA Report, Global Strategy For Asthma Management And Prevention. Updated April (2015). www.ginasthma.org

Jones SL, Herbison P, Cowan JO, et al. (Provide names of other authors) (2002). Exhaled NO and assessment of anti-inflammatory effects of inhaled steroid: dose-response relationship. Eur Respir J;20:601-8.

Kharitonov SA, Alving K, Barnes PJ (1997). Exhaled and nasal nitric oxide measurements: recommendations. Eur Respir J;10:1683–93

Kimberly B, Nejadnik B, Giraud GD, Holden WE (1996). Nasal contribution to exhaled nitric oxide at rest and during breathholding in humans. Am J Respir Crit Care Med;153:829-36.

Kumar SD, Emery MJ, Atkins ND, Danta I, Wanner A (1998). Airway mucosal blood flow in bronchial asthma. Am J Respir Crit Care Med; 158: 153-156

Leonardi S, Cuppari C, Lanzafame A, Attardo D, et al. (Provide names of other authors) (2015). Exhaled breath temperature in asthmatic children . J Biol Regul Homeost Agents. Apr-Jun; 29(2 Suppl 1):47-54.

Mattes J, Storm van's Gravesande K, Reining U, Alving K, et al. (Provide names of other authors) (1999). NO in exhaled air is correlated with markers of eosinophilic airway inflammation in corticosteroid dependent childhood asthma. Eur Respir J;13:1391-5

Melo R, Popov T, Sole D (2010). Exhaled breath temperature, a new biomarker in asthma control: a pilot study. J. bras. pneumol. ; 36,6

Paredi P, Kharitonov SA, Barnes PJ (2002). Faster rise of exhaled breath temperature in asthma: a novel marker of airway inflammation. Am J Respir Crit Care Med, 165:181-184

Paredi, P, Kharitonov, SA, Barnes, PJ (2005). Correlation of exhaled breath temperature with bronchial blood flow in asthma. Respir Res. ;6

Piacentini GL, Bodini A, Zerman L, Costella S, et al. (Provide names of other authors) (2002). Relationship between exhaled air temperature and exhaled nitric oxide in childhood asthma. Eur Respir J;20(1):108-11.

Piacentini, D. Peroni, E. Crestani, et al. (Provide names of other authors) (2007). Exhaled air temperature in asthma: methods and relationship with markers of disease. Clinical and Experimental Allergy. 37: 415–419

Robbins RA, Springall DR, Warren JB, Kwon OJ, Buttery LD, Wilson AJ, Adcock IM, Riveros-Moreno V, Moncada S, Polak J (1994). Inducible nitric oxide synthase is increased in murine lung epithelial cells by cytokine stimulation. Biochem Biophys Res Commun; 198: 835-843

Roslas PP,Dompeling E, Dentener MA et al. (Provide names of other authors) (2004). Childhood asthma : Exaled markers of airway inflammation , asthma control score, and lung function tests . Pediatr Pulmonol; 38:107-14

Series ‘‘ATS/ERS Task Force: Standardisation Of Lung Function Testing’’ Eur Respir J 2005; 26: 319–338

Spergel JM, Fogg MI, Bokszczanin-Knosala A (2005). Correlation of exhaled nitric oxide, spirometry and astma symptoms. J. Asthma;42:879-83.

Ullian ME (1999). The role of corticosteriods in the regulation of vascular tone. Cardiovasc Res, 41:55-64

Venturini G, Colasanti M, Fioravanti E, Bianchini A, Ascenzi P (1999). Direct effect of temperature on the catalytic activity of nitric oxide synthases types I, II, and III. Nitric Oxide; 3: 375-382

Xepapadaki P, Xatziioannou A, Chatzicharalambous M, Makrinioti H, Papadopoulos NG (2010). Exhaled breath temperature increases during mild exacerbations in children with virus-induced asthma. Int Arch Allergy Immunol.; 153(1):70-4