



**HAL**  
open science

## **EXHALED AIR TEMPERATURE IN CHILDREN WITH BRONCHOPULMONARY DYSPLASIA**

Silvia Carraro, Giorgio Piacentini, Marta Lusiani, Zeynep Seda Uyan, Marco  
Filippone, Maurizio Schiavon, Attilio Loris Boner, Eugenio Baraldi

► **To cite this version:**

Silvia Carraro, Giorgio Piacentini, Marta Lusiani, Zeynep Seda Uyan, Marco Filippone, et al.. EXHALED AIR TEMPERATURE IN CHILDREN WITH BRONCHOPULMONARY DYSPLASIA. *Pediatric Pulmonology*, 2010, 45 (12), pp.1240. 10.1002/ppul.21317 . hal-00566725

**HAL Id: hal-00566725**

**<https://hal.science/hal-00566725>**

Submitted on 17 Feb 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



**EXHALED AIR TEMPERATURE IN CHILDREN WITH BRONCHOPULMONARY DYSPLASIA**

Journal:	<i>Pediatric Pulmonology</i>
Manuscript ID:	PPUL-10-0007.R1
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	29-Apr-2010
Complete List of Authors:	Carraro, Silvia; University of Padova, Department of Pediatrics Piacentini, Giorgio; University of Verona, Department of Pediatrics Lusiani, Marta; University of Padova, Department of Pediatrics Uyan, Zeynep; University of Padova, Department of Pediatrics Filippone, Marco; University of Padova, Department of Pediatrics Schiavon, Maurizio; ULSS 16, Center for Sports Medicine and Physical Activity, Department of Social Health Boner, Attilio; University of Verona, Department of Pediatrics Baraldi, Eugenio; University of Padova, Pediatrics
Keywords:	bronchopulmonary dysplasia, asthma, exhaled air temperature, biomarkers



1  
2  
3  
4  
5 **EXHALED AIR TEMPERATURE IN CHILDREN WITH BRONCHOPULMONARY**  
6 **DYSPLASIA**  
7  
8  
9

10 Silvia Carraro<sup>1,2</sup>,MD, Giorgio Piacentini<sup>1,3</sup>,MD, Marta Lusiani<sup>2</sup>,MD, Zeynep S Uyan<sup>2</sup>,MD,  
11 Marco Filippone<sup>2</sup>,MD, Maurizio Schiavon<sup>4</sup>,MD, Attilio L Boner<sup>3</sup>,MD, Eugenio Baraldi<sup>2</sup>,MD.  
12  
13  
14  
15  
16

17  
18 <sup>1</sup>These authors contributed equally to the article

19 <sup>2</sup>Department of Pediatrics, University of Padova, Padova, Italy

20  
21 <sup>3</sup>Department of Pediatrics, University of Verona, Verona, Italy.

22  
23 <sup>4</sup>Center for Sports Medicine and Physical Activity, Department of Social Health, ULSS 16,  
24 Padova, Italy  
25  
26  
27

28  
29 **Corresponding author**

30  
31 Eugenio Baraldi, MD  
32 Department of Pediatrics  
33 Respiratory Medicine and Allergy Unit  
34 University of Padova  
35 Via Giustiniani 3  
36 35128 Padova, Italy  
37 Phone: +39 049 8213560  
38 Fax: +39 049 8213502  
39 **E-mail: baraldi@pediatria.unipd.it**  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50

51  
52 **Institution where the study was performed:** Department of Pediatrics, University of  
53 Padova  
54

55 **Financial support:** The work had no financial support

56 **Running title:** Exhaled air temperature in BPD  
57  
58  
59  
60

## ABSTRACT

**Background.** Because they have similar functional and clinical profiles, bronchopulmonary dysplasia (BPD) survivors are often treated as asthmatic patients. In truth, very little is known about the possible biochemical and inflammatory mechanisms playing a part in BPD survivors' lungs. The aim of this study was to measure exhaled breath temperature in BPD survivors by comparison with asthmatic cases and healthy controls.

**Methods.** Three groups of age-matched adolescents (n=17 each), i.e. BPD survivors (gestational ages < 31 weeks, birth weights < 1500 g), asthmatic subjects and healthy controls, underwent exhaled breath temperature and exhaled nitric oxide measurements, and spirometry.

**Results.** Exhaled breath temperature was significantly lower in the BPD survivors (26.72°C [25.11-27.57]) than in the asthmatic patients (29.60°C [29.20-30.02],  $p < 0.001$ ), while no significant difference emerged by comparison with healthy controls (26.97°C [26.58-27.38]). Considering the whole study population, a significant correlation was found between exhaled breath temperatures and exhaled nitric oxide concentrations ( $R = 0.42$ ,  $p = 0.004$ ). Spirometry revealed an obstructive lung function pattern in both the asthmatic cases and the BPD survivors, with lower parameters in the latter.

**Conclusions.** Exhaled breath temperatures and exhaled nitric oxide concentrations are significantly lower in BPD survivors than in asthmatic cases, suggesting that different pathogenetic mechanisms characterize these two chronic obstructive lung diseases.

**Keywords:** bronchopulmonary dysplasia; asthma; exhaled air temperature; biomarkers

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common form of chronic lung disease of prematurity. In childhood and adolescence, BPD survivors may have respiratory symptoms and lung function impairment that closely resemble those of asthmatic patients,<sup>1</sup> even if BPD patients present fewer acute exacerbations, poorer response to inhaled corticosteroids and less pronounced airway reversibility. A recent study reported that low-birth-weight survivors have significantly higher odds of hospitalization for respiratory diseases (wheezing, respiratory infections and respiratory failure) as young adults than their normal-birth-weight counterparts.<sup>2</sup>

Although there are no data to suggest an asthma-like inflammatory profile in the airways of BPD survivors, they are often empirically treated as if they were asthmatic (e.g. with glucocorticosteroids).<sup>3,4</sup> Very little is known, however, about the possible biochemical and inflammatory mechanisms involved in the pathogenesis of the symptoms and airway obstruction in BPD survivors,<sup>3</sup> and no data are available on the pathological features of these patients' lungs beyond infancy.<sup>3</sup>

It is common knowledge that asthma is a chronic inflammatory disease of the airways and several non-invasive biomarkers have been proposed for indirectly assessing different patterns of airway inflammation.<sup>5</sup> Exhaled nitric oxide has been studied the most and it is considered a reliable marker of eosinophilic inflammation in the airways.<sup>6,7</sup> Since "calor" is one of the cardinal signs of inflammation, some authors recently recommended considering exhaled air temperature as a potential marker of inflammation.<sup>8-9</sup> Increased values of exhaled breath temperature have been reported in children and adults with asthma,<sup>8-11</sup> correlating significantly with the concentrations of exhaled nitric oxide.<sup>8-10</sup> To our knowledge, no studies have evaluated exhaled air temperature in individuals with BPD.

1  
2  
3 The aim of the present cross-sectional study was to evaluate exhaled breath temperature  
4 (PLET, end-expiratory maneuver plateau temperature) in BPD survivors and to compare it  
5  
6 with the temperature measured in age-matched asthmatic subjects and healthy controls.  
7  
8  
9

## 10 11 12 13 14 15 **MATERIALS AND METHODS**

### 16 17 **Study subjects**

18  
19 BPD survivors: 17 BPD survivors were considered (table), drawn from a population with  
20 BPD born at gestational ages below 31 weeks and with birth weights under 1500 g  
21  
22 admitted to the Neonatal Intensive Care Unit between 1990 and 1994 and followed up  
23  
24 routinely thereafter at the Pediatrics Department in Padova. BPD was defined as oxygen  
25  
26 dependence persisting 28 days after birth in infants on mechanical ventilation (18 days on  
27  
28 average). At birth, the mean gestational age of the sample was 28.3 weeks (SD 1.9) and  
29  
30 the mean weight was 1011 g (SD 222).  
31  
32  
33  
34

35  
36 All the BPD survivors were clinically stable at the time of recruitment, 5 of them were on  
37  
38 low- to medium-dose inhaled steroid (ICS) treatment and two were being treated with  
39  
40 theophylline. Two of the BPD survivors were sensitive to common airborne allergens (dust  
41  
42 mites, dog and cat dander, grass and tree pollens).  
43  
44

45  
46 Asthmatic subjects: 17 allergic asthmatic adolescents (table) who had been born at term  
47  
48 were enrolled from among those regularly attending our outpatients clinic. Their asthma  
49  
50 had been diagnosed by a pediatric respiratory physician based on their clinical history  
51  
52 (cough, shortness of breath, recurrent wheezing, chest tightness) and an increase in FEV<sub>1</sub>  
53  
54 after salbutamol (400 µg) >12%, according to international guidelines.<sup>12</sup>  
55  
56

57  
58 All the asthmatic patients were clinically stable at the time of recruitment, 6 of them were  
59  
60 on low- to medium-dose inhaled steroid (ICS) treatment (100-200 mcg/day budesonide  
equivalent) and one of them was being treated with long-acting beta2 agonists too.

1  
2  
3 Healthy controls: 17 age-matched healthy adolescents (table) with no history of pre-term  
4  
5 birth, atopy or respiratory diseases were recruited as a control group.  
6

7  
8 For all three groups, subjects who had suffered any airway infections in the previous 4  
9  
10 weeks were excluded from the study.  
11

12 The Ethics Committee of our hospital reviewed and approved the protocol and all parents  
13  
14 gave their informed consent.  
15

16  
17 At recruitment, all the adolescents underwent physical examination, exhaled air  
18  
19 temperature measurement, FE<sub>NO</sub> measurement and spirometry. All the measurements  
20  
21 were performed in the afternoon. FE<sub>NO</sub> measurement was not possible in 3 subjects (1  
22  
23 with asthma and 2 with BPD)  
24  
25  
26

### 27 **Exhaled breath temperature (PLET)**

28  
29 Exhaled breath temperature (end-expiratory maneuver plateau temperature, PLET) was  
30  
31 measured as described elsewhere.<sup>13</sup> The environmental conditions were controlled in  
32  
33 order to maintain a stable temperature of 23±1 °C and a relative humidity of 40-50%.  
34

35  
36 The measurements were repeated three times. The inspiratory air stream temperature was  
37  
38 recorded during a complete inhalation to total lung capacity (TLC). The exhaled airway  
39  
40 temperature was measured during a slow exhalation to residual volume (RV) using the  
41  
42 Medical Mass Flow Sensor of the Vmax Spectra 229 Pulmonary Function Laboratory  
43  
44 (VIASYS Healthcare, Yorba Linda, CA, USA). Dynamic airway temperature and airflow  
45  
46 were measured with the Mass Flow Sensor. The response time of the Mass Flow Sensor  
47  
48 to a steep change in airway temperature was approximately 64 milliseconds, with a  
49  
50 thermal resolution of 0.01°C. Mouth pressure was measured at the airway opening using a  
51  
52 differential pressure transducer. Exhaled flow was directed through an alternate pathway  
53  
54 with a fixed resistor in place to control the expiratory air flow rate and maintain an airway  
55  
56 pressure sufficient to keep the velum closed and prevent any contribution of warmed gas  
57  
58 from nasal sinuses. A mouth pressure of > 5 cm H<sub>2</sub>O also helped the subject to stabilize  
59  
60

1  
2  
3 the expiratory flow at 5-6 l/min. All the signals, including exhaled air temperature, mouth  
4 pressure and exhalation flow rate, were transferred to a personal computer and analyzed  
5 using software specifically developed for this purpose (Vmax Temperature, VIASYS  
6 Healthcare, Yorba Linda, CA, USA). Real-time signal display consisted of inspiratory and  
7 expiratory airway temperature, respiratory flow rate and mouth (airway) pressure on a time  
8 axis. Flow and pressure limit indicators were presented on screen as a coaching aid.  
9

10  
11  
12  
13  
14  
15  
16  
17 At the end of the test, the software automatically calculated the PLET, which was the  
18 parameter used to compare the groups.  
19

### 20 21 22 23 **Fractional exhaled nitric oxide (FE<sub>NO</sub>) and pulmonary function measurement**

24  
25  
26 FE<sub>NO</sub> was measured using the NIOX system (Aerocrine, Stockholm, Sweden), according  
27 to the ERS/ATS guidelines for measuring FE<sub>NO</sub> in children.<sup>14</sup> Children inhaled NO-free air  
28 to total lung capacity (TLC) and exhaled through a dynamic flow restrictor with a target  
29 flow of 50 ml/sec for at least 6-7 seconds. No nose clip was used. The NIOX system was  
30 calibrated using a 200 ppb NO tank (Lindegas Hoek Loos Speciality Gases, Amsterdam,  
31 Netherlands) according to the manufacturer's instructions.  
32

33  
34  
35  
36  
37  
38  
39  
40 Lung function was measured by means of a 10-liter bell spirometer (Biomedin, Padova,  
41 Italy) and the best of three maneuvers was expressed as a percentage (%) of the  
42 predicted reference values, according to the ERS/ATS guidelines.<sup>15</sup>  
43  
44  
45

### 46 47 **Statistical analysis**

48  
49  
50 It has been calculated that a sample size of 17 subjects allows detecting a 1 °C difference  
51 between groups of with a power of 80% at a 2-sided  $\alpha$ -level of .05.  
52

53  
54  
55 Age and anthropometric data were expressed as the mean and standard deviation (SD)  
56 (table).  
57

58  
59  
60 Since PLET, FE<sub>NO</sub> and lung function data were not normally distributed (as demonstrated  
by the Shapiro-Wilk test), they were expressed as medians and interquartile ranges (IQR),



1  
2  
3 and analyzed by means of non-parametric tests. Differences between groups were  
4  
5 analyzed using the Kruskal-Wallis test, followed (where significant) by the Mann-Whitney  
6  
7 U-test for comparisons between groups. Correlations were evaluated using Spearman's  
8  
9 rank test. Statistical significance was set at a 2-sided alpha level of 0.05.  
10  
11

## 12 13 14 15 **RESULTS**

### 16 17 **Exhaled breath temperature (PLET)**

18  
19 The Kruskal Wallis test revealed a significant difference in the PLET for the 3 groups  
20  
21 ( $p < 0.001$ ) (figure 1A). The between-group comparison found a significantly lower PLET in  
22  
23 BPD survivors ( $26.72^{\circ}\text{C}$  [25.11-27.57]) than in asthmatic patients ( $29.60^{\circ}\text{C}$  [29.20-30.02],  
24  
25  $p < 0.001$ ), while no significant difference emerged between BPD survivors and healthy  
26  
27 controls ( $26.97^{\circ}\text{C}$  [26.58-27.38]  $p = 0.23$ ). The asthmatic cases had a significantly higher  
28  
29 PLET than the healthy controls ( $p < 0.001$ ).  
30  
31  
32

### 33 34 **Exhaled nitric oxide (FE<sub>NO</sub>)**

35  
36 The Kruskal Wallis test found a significant difference in FE<sub>NO</sub> for the 3 groups ( $p = 0.003$ )  
37  
38 (figure 1B). The between-group comparison revealed a significantly higher FE<sub>NO</sub> in  
39  
40 asthmatic cases (29.9 ppb [15.0-49.2]) than in either healthy controls (11.7 ppb [8.5-16.8],  
41  
42  $p = 0.008$ ) or BPD survivors (10.6 ppb [7.0-13.2],  $p = 0.002$ ), with no significant difference  
43  
44 between the latter two groups ( $p = 0.28$ ).  
45  
46  
47

### 48 49 **Lung function**

50  
51 The Kruskal Wallis test disclosed significant differences in all the spirometric parameters.  
52  
53 The between-group comparison showed that BPD children had lower FVC, FEV<sub>1</sub>, FEF<sub>25-75</sub>  
54  
55 and FEV<sub>1</sub>/FVC than either asthmatic cases or healthy controls; and the asthmatic cases  
56  
57 had lower FEV<sub>1</sub>, FEF<sub>25-75</sub> and FEV<sub>1</sub>/FVC than healthy controls (table, figure 1C and 1D).  
58  
59  
60

## Correlations

Considering the whole sample, a significant correlation emerged between PLET and  $FE_{NO}$  ( $R=0.42$   $p=0.004$ ) (figure 2).

In BPD survivors there was a correlation approaching statistical significance between FVC and PLET ( $p=0.058$   $R=0.47$ ), which was stronger considering the whole sample ( $R=0.28$   $p=0.036$ ).

None of the other spirometric parameters correlated with PLET values in BPD survivors.

No significant correlations emerged between spirometric measurements and PLET in asthmatic cases or healthy controls.

## DISCUSSION

This study shows that exhaled breath temperature is significantly lower in BPD survivors than in asthmatic patients.

BPD survivors have respiratory symptoms and lung function profiles that resemble those of asthmatic children<sup>16</sup> and this explains why they are often considered and empirically treated as asthmatic patients during their childhood.<sup>3</sup> Very little it is known about the processes underlying the obstructive lung function pattern in BPD survivors and there is no evidence to support any asthma-like inflammation in this condition.<sup>4,17,18</sup>

Here we demonstrate that both PLET and  $FE_{NO}$  are lower in BPD survivors than in asthmatic children, suggesting that the two conditions have a different pathogenesis (figure 1A and 1B). In a previous study, we already showed that exhaled NO is lower in BPD survivors than in asthmatic cases;<sup>19</sup> the present study further supports the lack of any asthma-like airway inflammation in BPD survivors. A possible limit in the interpretation of our results is the potential effect of ICS treatment and atopy on PLET values. In fact while all asthmatic patients were allergic, only two BPD patients were sensitized. In addition some patients in both groups were treated with ICS.

1  
2  
3 In keeping with previous studies conducted on asthmatic patients,<sup>8-9</sup> PLET and FE<sub>NO</sub>  
4 correlated significantly. It is worth noting that the scatter plot (figure 2) shows a clear  
5 separation between asthmatic cases and BPD survivors, again suggesting that different  
6 pathogenetic mechanisms underlie these two chronic obstructive lung diseases.  
7  
8

9  
10  
11  
12 As previously reported,<sup>8-10</sup> asthmatic subjects have higher levels of both FE<sub>NO</sub> and PLET,  
13 which are thought to reflect eosinophilic airway inflammation.<sup>6,20</sup> The higher exhaled breath  
14 temperature in asthmatic subjects also seems to suggest an increased vascularity and  
15 bronchial blood flow.<sup>10</sup> In BPD survivors, on the other hand, PLET and FE<sub>NO</sub> are  
16 significantly lower than in asthmatic patients and even tend to be lower than in healthy  
17 controls, although without reaching the statistical significance (figure 1A and 1B). This  
18 trend could be explained by the anatomical alterations that characterize BPD lungs,  
19 namely alveolar simplification, variable degree of interstitial fibrosis<sup>21,22</sup> and dysmorphic  
20 vascular growth.<sup>23</sup> These anatomical alterations might presumably be responsible for an  
21 impaired heat exchange between the bronchial vessels and the airway lumen, giving rise  
22 to normal-to-low values of exhaled air temperature in BPD survivors.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 As previously reported,<sup>24</sup> we confirm here that BPD survivors have a lung function pattern  
39 with airflow limitation (figure 1C). An autoptic study demonstrated thickening of the airway  
40 walls and an increase in smooth muscle, suggesting that these aspects may have a role in  
41 airway obstruction and hyper-responsiveness in BPD survivors.<sup>25</sup> Moreover BPD survivors  
42 have a significantly reduced forced vital capacity (figure 1D). This last features might be  
43 explained by the impaired growth of the BPD survivor's lungs, which would lead to reduced  
44 pulmonary volumes. Previous studies have already documented in BPD survivors an  
45 impaired lung function.<sup>24,26,27</sup> It may be that lung function impairment in BPD survivors is  
46 not just the static outcome of the initial damage, but due to an ongoing  
47 remodeling/damaging process. Although our findings go against any suggestion of an  
48 asthma-like eosinophilic inflammatory profile, other inflammatory pathways (e.g.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 neutrophilic or lymphocytic) and/or remodeling mechanisms may be involved. Elucidating  
4  
5 this pathophysiological substrate could have an impact on the long-term management of  
6  
7 BPD subjects.  
8  
9

10 In conclusion, we showed that exhaled breath temperature (PLET) and exhaled nitric  
11  
12 oxide (which are considered biomarkers of airway inflammation) are not increased in BPD  
13  
14 survivors. Further studies are needed to assess the role of other non-invasive biomarkers,  
15  
16 as measured for instance in exhaled breath condensate, to shed light on the pathogenic  
17  
18 processes affecting the BPD survivor's lung and thus pave the way to the development of  
19  
20 new, specifically targeted drugs.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

### 31 **Acknowledgement**

32  
33 The authors thank VIASYS Healthcare, Yorba Linda, CA, USA, for providing hardware and  
34  
35 software for exhaled air evaluation.  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Greenough A. Bronchopulmonary dysplasia--long term follow up. *Paediatr Respir Rev* 2006;7:S189-91.
2. Walter EC, Ehlenbach WJ, Hotchkin DL, Chien JW, Koepsell TD. Low Birthweight and Respiratory Disease in Adulthood: A Population-Based Case-Control Study. *Am J Respir Crit Care Med* 2009;180:176-80
3. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007;357:1946-1955.
4. Narang I, Baraldi E, Silverman M, Bush A. Airway function measurements and the long-term follow-up of survivors of preterm birth with and without chronic lung disease. *Pediatr Pulmonol* 2006;41:497-508.
5. Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. *Am J Respir Crit Care Med* 2001;163:1693-1722.
6. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;35:1175-1179.
7. Baraldi E, Azzolin NM, Zanconato S, Dario C, Zacchello F. Corticosteroids decrease exhaled nitric oxide in children with acute asthma. *J Pediatr* 1997;131:381-385.
8. 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.
9. 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.

- 1  
2  
3 10. Paredi P, Kharitonov SA, Barnes PJ. Correlation of exhaled breath temperature with  
4  
5 bronchial blood flow in asthma. *Respir Res* 2005 ;6:15.  
6  
7
- 8 11. Pifferi M, Ragazzo V, Previti A, Pioggia G, Ferro M, Macchia P, Piacentini GL,  
9  
10 Boner AL. Exhaled air temperature in asthmatic children: a mathematical  
11  
12 evaluation. *Pediatr Allergy Immunol* 2009;20:164-171.  
13  
14
- 15 12. Global Strategy for Asthma Management and Prevention, Global Initiative for  
16  
17 Asthma (GINA) 2008. Available from: <http://www.ginasthma.org>.  
18  
19
- 20 13. Piacentini GL, Peroni D, Crestani E, Zardini F, Bodini A, Costella S, Boner AL.  
21  
22 Exhaled air temperature in asthma: methods and relationship with markers of  
23  
24 disease. *Clin Exp Allergy* 2007;37:415-419  
25  
26
- 27 14. Baraldi E, de Jongste JC; European Respiratory Society; American Thoracic  
28  
29 Society. Measurement of exhaled nitric oxide in children, 2001. *Eur Respir J*  
30  
31 2002;20:223-237.  
32  
33
- 34 15. Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of  
35  
36 spirometry. *Eur Respir J* 2005 ; 26:319-338.  
37  
38
- 39 16. Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory  
40  
41 health in prematurely born preschool children with and without bronchopulmonary  
42  
43 dysplasia. *J Pediatr* 2007;150:256-261.  
44  
45
- 46 17. Allen J, Zwerdling R, Ehrenkranz R, et al. Statement on the care of the child with  
47  
48 chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med*  
49  
50 2003;168:356-396  
51  
52
- 53 18. Bhandari A, Bhandari V. Pitfalls, problems, and progress in bronchopulmonary  
54  
55 dysplasia. *Pediatrics* 2009;123:1562-1573  
56  
57
- 58 19. Baraldi E, Bonetto G, Zacchello F, Filippone M. Low exhaled nitric oxide in school-  
59  
60 age children with bronchopulmonary dysplasia and airflow limitation. *Am J Respir  
Crit Care Med* 2005;171:68-72.

- 1  
2  
3 20. Piacentini GL, Bodini A, Peroni D, Ress M, Costella S, Boner AL. Exhaled air  
4 temperature and eosinophil airway inflammation in allergic asthmatic children. *J*  
5  
6 Allergy Clin Immunol 2004;114:202-204.  
7  
8  
9  
10 21. Thébaud B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels  
11 gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit*  
12  
13 Care Med 2007;175:978-985.  
14  
15  
16  
17 22. Coalson JJ. Pathology of bronchopulmonary dysplasia. *Semin Perinatol*  
18  
19 2006;30:179-184.  
20  
21  
22 23. Abman SH. The dysmorphic pulmonary circulation in bronchopulmonary dysplasia:  
23 a growing story. *Am J Respir Crit Care Med* 2008;178:114-115  
24  
25  
26  
27 24. Filippone M, Sartor M, Zacchello F, Baraldi E. Flow limitation in infants with  
28 bronchopulmonary dysplasia and respiratory function at school age. *Lancet*  
29  
30 2003;361:753-754.  
31  
32  
33  
34 25. Tiddens HA, Hofhuis W, Casotti V, Hop WC, Hulsmann AR, de Jongste JC. Airway  
35 dimensions in bronchopulmonary dysplasia: implications for airflow obstruction.  
36  
37 *Pediatr Pulmonol* 2008;43:1206-13.  
38  
39  
40  
41 26. Jacob SV, Coates AL, Lands LC, MacNeish CF, Riley SP, Hornby L, Outerbridge  
42 EW, Davis GM, Williams RL. Long-term pulmonary sequelae of severe  
43 bronchopulmonary dysplasia. *J Pediatr* 1998;133:193-200.  
44  
45  
46  
47  
48 27. Gross SJ, Iannuzzi DM, Kveselis DA, Anbar RD. Effect of preterm birth on  
49 pulmonary function at school age: a prospective controlled study. *J Pediatr*  
50  
51 1998;133:188-192.  
52  
53  
54  
55  
56  
57  
58  
59  
60

**FIGURE LEGENDS**

**Figure 1.** Panel A shows PLET values in the 3 groups; panel B shows FE<sub>NO</sub> values in the 3 groups; panel C shows FVC values in the 3 groups; panel D shows FEV1 values in the 3 groups. \*\*p<0.001 and \*p<0.01 vs healthy controls; #p<0.05 and §p<0.01 vs asthmatic subjects; γ p<0.001 vs BPD survivors

**Figure 2.** Correlation between FE<sub>NO</sub> values and PLET values in BPD, asthmatic and healthy subjects (R=0.42 p=0.004).

For Peer Review



1  
2  
3  
4  
5 **EXHALED AIR TEMPERATURE IN CHILDREN WITH BRONCHOPULMONARY**  
6 **DYSPLASIA**  
7  
8  
9

10 Silvia Carraro<sup>1,2</sup>,MD, Giorgio Piacentini<sup>1,3</sup>,MD, Marta Lusiani<sup>2</sup>,MD, Zeynep S Uyan<sup>2</sup>,MD,  
11 Marco Filippone<sup>2</sup>,MD, Maurizio Schiavon<sup>4</sup>,MD, Attilio L Boner<sup>3</sup>,MD, Eugenio Baraldi<sup>2</sup>,MD.  
12  
13  
14  
15  
16

17  
18 <sup>1</sup>These authors contributed equally to the article

19 <sup>2</sup>Department of Pediatrics, University of Padova, Padova, Italy

20  
21 <sup>3</sup>Department of Pediatrics, University of Verona, Verona, Italy.

22  
23 <sup>4</sup>Center for Sports Medicine and Physical Activity, Department of Social Health, ULSS 16,  
24 Padova, Italy  
25  
26  
27

28  
29 **Corresponding author**  
30

31 Eugenio Baraldi, MD  
32 Department of Pediatrics  
33 Respiratory Medicine and Allergy Unit  
34 University of Padova  
35 Via Giustiniani 3  
36 35128 Padova, Italy  
37 Phone: +39 049 8213560  
38 Fax: +39 049 8213502  
39 **E-mail: baraldi@pediatria.unipd.it**  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51

52 **Institution where the study was performed:** Department of Pediatrics, University of  
53 Padova  
54

55 **Financial support:** The work had no financial support

56 **Running title:** Exhaled air temperature in BPD  
57  
58  
59  
60

## ABSTRACT

**Background.** Because they have similar functional and clinical profiles, bronchopulmonary dysplasia (BPD) survivors are often treated as asthmatic patients. In truth, very little is known about the possible biochemical and inflammatory mechanisms playing a part in BPD survivors' lungs. The aim of this study was to measure exhaled breath temperature (~~an indirect marker of airway inflammation~~) in BPD survivors by comparison with asthmatic cases and healthy controls.

**Methods.** Three groups of age-matched adolescents (n=17 each), i.e. BPD survivors (gestational ages < 31 weeks, birth weights < 1500 g), asthmatic subjects and healthy controls, underwent exhaled breath temperature and exhaled nitric oxide measurements, and spirometry.

**Results.** Exhaled breath temperature was significantly lower in the BPD survivors (26.72°C [25.11-27.57]) than in the asthmatic patients (29.60°C [29.20-30.02],  $p < 0.001$ ), while no significant difference emerged by comparison with healthy controls (26.97°C [26.58-27.38]). Considering the whole study population, a significant correlation was found between exhaled breath temperatures and exhaled nitric oxide concentrations ( $R = 0.42$ ,  $p = 0.004$ ). Spirometry revealed an obstructive lung function pattern in both the asthmatic cases and the BPD survivors, with lower parameters in the latter.

**Conclusions.** Exhaled breath temperatures and exhaled nitric oxide concentrations are significantly lower in BPD survivors than in asthmatic cases, suggesting that different pathogenetic mechanisms characterize these two chronic obstructive lung diseases.

**Keywords:** bronchopulmonary dysplasia; asthma; exhaled air temperature; biomarkers

## INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common form of chronic lung disease of prematurity. In childhood and adolescence, BPD survivors may have respiratory symptoms and lung function impairment that closely resemble those of asthmatic patients,<sup>1</sup> **even if BPD patients present fewer acute exacerbations, poorer response to inhaled corticosteroids and less pronounced airway reversibility** ~~though they do not share the same origins.~~ A recent study reported that low-birth-weight survivors have significantly higher odds of hospitalization for respiratory diseases (wheezing, respiratory infections and respiratory failure) as young adults than their normal-birth-weight counterparts.<sup>2</sup>

Although there are no data to suggest an asthma-like inflammatory profile in the airways of BPD survivors, they are often empirically treated as if they were asthmatic (e.g. with glucocorticosteroids).<sup>3,4</sup> Very little is known, however, about the possible biochemical and inflammatory mechanisms involved in the pathogenesis of the symptoms and airway obstruction in BPD survivors,<sup>3</sup> and no data are available on the pathological features of these patients' lungs beyond infancy.<sup>3</sup>

It is common knowledge that asthma is a chronic inflammatory disease of the airways and several non-invasive biomarkers have been proposed for indirectly assessing different patterns of airway inflammation.<sup>5</sup> Exhaled nitric oxide has been studied the most and it is considered a reliable marker of eosinophilic inflammation in the airways.<sup>6,7</sup> Since "calor" is one of the cardinal signs of inflammation, some authors recently recommended considering exhaled air temperature as a potential marker of inflammation.<sup>8-9</sup> Increased values of exhaled breath temperature have been reported in children and adults with asthma,<sup>8-11</sup> correlating significantly with the concentrations of exhaled nitric oxide.<sup>8-10</sup> To our knowledge, no studies have evaluated exhaled air temperature in individuals with BPD.

1  
2  
3 The aim of the present **cross-sectional** study was to evaluate exhaled breath temperature  
4  
5 (PLET, end-expiratory maneuver plateau temperature) in BPD survivors and to compare it  
6  
7  
8 with the temperature measured in age-matched asthmatic subjects and healthy controls.  
9

## 10 11 12 13 14 15 **MATERIALS AND METHODS**

### 16 17 **Study subjects**

18  
19 BPD survivors: 17 BPD survivors were considered (**table**), drawn from a population with  
20  
21 BPD born at gestational ages below 31 weeks and with birth weights under 1500 g  
22  
23 admitted to the Neonatal Intensive Care Unit between 1990 and 1994 and followed up  
24  
25 routinely thereafter at the Pediatrics Department in Padova. BPD was defined as oxygen  
26  
27 dependence persisting 28 days after birth in infants on mechanical ventilation (18 days on  
28  
29 average). At birth, the mean gestational age of the sample was 28.3 weeks (SD 1.9) and  
30  
31 the mean weight was 1011 g (SD 222).  
32  
33

34  
35 All the BPD survivors were clinically stable at the time of recruitment, 5 of them were on  
36  
37 low- to medium-dose inhaled steroid treatment and two were being treated with  
38  
39 theophylline. Two of the BPD survivors were sensitive to common airborne allergens (dust  
40  
41 mites, dog and cat dander, grass and tree pollens).  
42  
43

44  
45 Asthmatic subjects: 17 allergic asthmatic adolescents (**table**) who had been born at term  
46  
47 were enrolled from among those regularly attending our outpatients clinic. Their asthma  
48  
49 had been diagnosed by a pediatric respiratory physician based on their clinical history  
50  
51 (cough, shortness of breath, recurrent wheezing, chest tightness) and an increase in FEV<sub>1</sub>  
52  
53 after salbutamol (400 µg) >12%, according to international guidelines.<sup>12</sup>  
54  
55

56  
57 All the asthmatic patients were clinically stable at the time of recruitment, 6 of them were  
58  
59 on low- to medium-dose inhaled steroid treatment (100-200 mcg/day budesonide  
60  
equivalent) and one of them was being treated with long-acting beta2 agonists too.

1  
2  
3 Healthy controls: 17 age-matched healthy adolescents (table) with no history of pre-term  
4  
5 birth, atopy or respiratory diseases were recruited as a control group.  
6

7  
8 For all three groups, subjects who had suffered any airway infections in the previous 4  
9  
10 weeks were excluded from the study.  
11

12 The Ethics Committee of our hospital reviewed and approved the protocol and all parents  
13  
14 gave their informed consent.  
15

16  
17 At recruitment, all the adolescents underwent physical examination, exhaled air  
18  
19 temperature measurement, FE<sub>NO</sub> measurement and spirometry. All the measurements  
20  
21 were performed in the afternoon. FE<sub>NO</sub> measurement was not possible in 3 subjects (1  
22  
23 with asthma and 2 with BPD)  
24  
25  
26

### 27 **Exhaled breath temperature (PLET)**

28  
29 Exhaled breath temperature (end-expiratory maneuver plateau temperature, PLET) was  
30  
31 measured as described elsewhere.<sup>13</sup> The environmental conditions were controlled in  
32  
33 order to maintain a stable temperature of 23±1 °C and a relative humidity of 40-50%.  
34

35  
36 The measurements were repeated three times. The inspiratory air stream temperature was  
37  
38 recorded during a complete inhalation to total lung capacity (TLC). The exhaled airway  
39  
40 temperature was measured during a slow exhalation to residual volume (RV) using the  
41  
42 Medical Mass Flow Sensor of the Vmax Spectra 229 Pulmonary Function Laboratory  
43  
44 (VIASYS Healthcare, Yorba Linda, CA, USA). Dynamic airway temperature and airflow  
45  
46 were measured with the Mass Flow Sensor. The response time of the Mass Flow Sensor  
47  
48 to a steep change in airway temperature was approximately 64 milliseconds, with a  
49  
50 thermal resolution of 0.01°C. Mouth pressure was measured at the airway opening using a  
51  
52 differential pressure transducer. Exhaled flow was directed through an alternate pathway  
53  
54 with a fixed resistor in place to control the expiratory air flow rate and maintain an airway  
55  
56 pressure sufficient to keep the velum closed and prevent any contribution of warmed gas  
57  
58 from nasal sinuses. A mouth pressure of > 5 cm H<sub>2</sub>O also helped the subject to stabilize  
59  
60

1  
2  
3 the expiratory flow at 5-6 l/min. All the signals, including exhaled air temperature, mouth  
4 pressure and exhalation flow rate, were transferred to a personal computer and analyzed  
5 using software specifically developed for this purpose (Vmax Temperature, VIASYS  
6 Healthcare, Yorba Linda, CA, USA). Real-time signal display consisted of inspiratory and  
7 expiratory airway temperature, respiratory flow rate and mouth (airway) pressure on a time  
8 axis. Flow and pressure limit indicators were presented on screen as a coaching aid.  
9

10  
11  
12  
13  
14  
15  
16  
17 At the end of the test, the software automatically calculated the PLET, which was the  
18 parameter used to compare the groups.  
19

### 20 21 22 **Fractional exhaled nitric oxide (FE<sub>NO</sub>) and pulmonary function measurement**

23  
24  
25  
26 FE<sub>NO</sub> was measured using the NIOX system (Aerocrine, Stockholm, Sweden), according  
27 to the ERS/ATS guidelines for measuring FE<sub>NO</sub> in children.<sup>14</sup> Children inhaled NO-free air  
28 to total lung capacity (TLC) and exhaled through a dynamic flow restrictor with a target  
29 flow of 50 ml/sec for at least 6-7 seconds. No nose clip was used. The NIOX system was  
30 calibrated using a 200 ppb NO tank (Lindegas Hoek Loos Speciality Gases, Amsterdam,  
31 Netherlands) according to the manufacturer's instructions.  
32

33  
34  
35  
36  
37  
38  
39  
40 Lung function was measured by means of a 10-liter bell spirometer (Biomedin, Padova,  
41 Italy) and the best of three maneuvers was expressed as a percentage (%) of the  
42 predicted reference values, according to the ERS/ATS guidelines.<sup>15</sup>  
43  
44  
45

### 46 47 **Statistical analysis**

48  
49  
50 It has been calculated that a sample size of 17 subjects allows detecting a 1 °C difference  
51 between groups of with a power of 80% at a 2-sided  $\alpha$ -level of .05.  
52

53  
54  
55 Age and anthropometric data were expressed as the mean and standard deviation (SD)  
56 (table).  
57

58  
59 Since PLET, FE<sub>NO</sub> and lung function data were not normally distributed (as demonstrated  
60 by the Shapiro-Wilk test), they were expressed as medians and interquartile ranges (IQR),

1  
2  
3 and analyzed by means of non-parametric tests. Differences between groups were  
4  
5 analyzed using the Kruskal-Wallis test, followed (where significant) by the Mann-Whitney  
6  
7 U-test for comparisons between groups. Correlations were evaluated using Spearman's  
8  
9 rank test. Statistical significance was set at a 2-sided  $\alpha$  level of 0.05.  
10  
11

## 12 13 14 15 **RESULTS**

### 16 17 **Exhaled breath temperature (PLET)**

18  
19 The Kruskal Wallis test revealed a significant difference in the PLET for the 3 groups  
20  
21 ( $p < 0.001$ ) (figure 1A). The between-group comparison found a significantly lower PLET in  
22  
23 BPD survivors (26.72°C [25.11-27.57]) than in asthmatic patients (29.60°C [29.20-30.02],  
24  
25  $p < 0.001$ ), while no significant difference emerged between BPD survivors and healthy  
26  
27 controls (26.97°C [26.58-27.38]  $p = 0.23$ ). The asthmatic cases had a significantly higher  
28  
29 PLET than the healthy controls ( $p < 0.001$ ).  
30  
31  
32

### 33 34 **Exhaled nitric oxide (FE<sub>NO</sub>)**

35  
36 The Kruskal Wallis test found a significant difference in FE<sub>NO</sub> for the 3 groups ( $p = 0.003$ )  
37  
38 (figure 1B). The between-group comparison revealed a significantly higher FE<sub>NO</sub> in  
39  
40 asthmatic cases (29.9 ppb [15.0-49.2]) than in either healthy controls (11.7 ppb [8.5-16.8],  
41  
42  $p = 0.008$ ) or BPD survivors (10.6 ppb [7.0-13.2],  $p = 0.002$ ), with no significant difference  
43  
44 between the latter two groups ( $p = 0.28$ ).  
45  
46  
47

### 48 49 **Lung function**

50  
51 The Kruskal Wallis test disclosed significant differences in all the spirometric parameters.  
52  
53 The between-group comparison showed that BPD children had lower FVC, FEV<sub>1</sub>, FEF<sub>25-75</sub>  
54  
55 and FEV<sub>1</sub>/FVC than either asthmatic cases or healthy controls; and the asthmatic cases  
56  
57 had lower FEV<sub>1</sub>, FEF<sub>25-75</sub> and FEV<sub>1</sub>/FVC than healthy controls (table, figure 1C and 1D).  
58  
59  
60

## Correlations

Considering the whole sample, a significant correlation emerged between PLET and  $FE_{NO}$  ( $R=0.42$   $p=0.004$ ) (figure 2).

In BPD survivors there was a correlation approaching statistical significance between FVC and PLET ( $p=0.058$   $R=0.47$ ), which was stronger considering the whole sample ( $R=0.28$   $p=0.036$ ) whereas none of the other spirometric parameters correlated with PLET values in BPD survivors.

No significant correlations emerged between spirometric measurements and PLET in asthmatic cases or healthy controls.

## DISCUSSION

This study shows that exhaled breath temperature is significantly lower in BPD survivors than in asthmatic patients.

BPD survivors have respiratory symptoms and lung function profiles that resemble those of asthmatic children<sup>16</sup> and this explains why they are often considered and empirically treated as asthmatic patients during their childhood.<sup>3</sup> Very little it is known about the processes underlying the obstructive lung function pattern in BPD survivors and there is no evidence to support any asthma-like inflammation in this condition.<sup>4,17,18</sup>

Here we demonstrate that both PLET and  $FE_{NO}$  are lower in BPD survivors than in asthmatic children, strongly suggesting that the two conditions have a different pathogenesis (figure 1A and 1B). In a previous study, we already showed that exhaled NO is lower in BPD survivors than in asthmatic cases;<sup>19</sup> the present study further supports the lack of any asthma-like airway inflammation in BPD survivors.

A possible limit in the interpretation of our results is the potential effect of ICS treatment and atopy on PLET values. In fact while all asthmatic patients were allergic, only two BPD patients were sensitized. In addition some patients in both groups were treated with ICS.



1  
2  
3 In keeping with previous studies conducted on asthmatic patients,<sup>8-9</sup> PLET and FE<sub>NO</sub>  
4 correlated significantly. It is worth noting that the scatter plot (figure 2) shows a clear  
5 separation between asthmatic cases and BPD survivors, again suggesting that different  
6 pathogenetic mechanisms underlie these two chronic obstructive lung diseases.  
7  
8

9  
10  
11  
12 As previously reported,<sup>8-10</sup> asthmatic subjects have higher levels of both FE<sub>NO</sub> and PLET,  
13 which are thought to reflect eosinophilic airway inflammation.<sup>6,20</sup> The higher exhaled breath  
14 temperature in asthmatic subjects also seems to suggest an increased vascularity and  
15 bronchial blood flow.<sup>10</sup> In BPD survivors, on the other hand, PLET and FE<sub>NO</sub> are  
16 significantly lower than in asthmatic patients and even tend to be lower than in healthy  
17 controls, although without reaching the statistical significance (figure 1A and 1B). This  
18 trend could be explained by the anatomical alterations that characterize BPD lungs,  
19 namely alveolar simplification, variable degree of interstitial fibrosis<sup>21,22</sup> and dysmorphic  
20 vascular growth.<sup>23</sup> **These anatomical alterations might presumably be responsible for an  
21 impaired heat exchange between the bronchial vessels and the airway lumen, giving rise  
22 to normal-to-low values of exhaled air temperature in BPD survivors.**  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 As previously reported,<sup>24</sup> we confirm here that BPD survivors have a lung function pattern  
39 with airflow limitation (figure 1C). An autoptic study demonstrated thickening of the airway  
40 walls and an increase in smooth muscle, suggesting that these aspects may have a role in  
41 airway obstruction and hyper-responsiveness in BPD survivors.<sup>25</sup> Moreover BPD survivors  
42 have a significantly reduced forced vital capacity (figure 1D). This last features might be  
43 explained by the impaired growth of the BPD survivor's lungs, which would lead to reduced  
44 pulmonary volumes.  
45  
46  
47  
48  
49  
50  
51  
52  
53

54 Previous studies have already documented an impaired lung function in BPD survivors **an  
55 impaired lung function and characterized by an accelerated decline.**<sup>24,26,27</sup> ~~In a follow-up  
56 study, Doyle et al.<sup>28</sup> reported significant airflow obstruction in BPD survivors at 18 years of  
57 age, with an accelerated decline in their FEV<sub>1</sub>/FVC ratio, suggesting an earlier~~  
58  
59  
60

1  
2  
3 deterioration in their respiratory health than in the general population. Lung function  
4 declines physiologically in adulthood and senescence, albeit without reaching levels  
5 associated with disability.<sup>29</sup> This decline could be more of a problem in BPD survivors,  
6 whose maximal lung function is underdeveloped. It may be that lung function impairment in  
7 BPD survivors is not just the static outcome of the initial damage, but due to an ongoing  
8 remodeling/damaging process. Although our findings go against any suggestion of an  
9 asthma-like eosinophilic inflammatory profile, other inflammatory pathways (e.g.  
10 neutrophilic or lymphocytic) and/or remodeling mechanisms may be involved. Elucidating  
11 this pathophysiological substrate could have a **great** impact on the long-term management  
12 of BPD subjects.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26

27 In conclusion, we showed that exhaled breath temperature (PLET) and exhaled nitric  
28 oxide (which are considered biomarkers of eosinophilic airway inflammation) are not  
29 increased in BPD survivors. Further studies are needed to assess the role of other non-  
30 invasive biomarkers, as measured for instance in exhaled breath condensate, to shed light  
31 on the pathogenic processes affecting the BPD survivor's lung and thus pave the way to  
32 the development of new, specifically targeted drugs.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

### 50 **Acknowledgement**

51 The authors thank VIASYS Healthcare, Yorba Linda, CA, USA, for providing hardware and  
52 software for exhaled air evaluation.  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Greenough A. Bronchopulmonary dysplasia--long term follow up. *Paediatr Respir Rev* 2006;7:S189-91.
2. Walter EC, Ehlenbach WJ, Hotchkin DL, Chien JW, Koepsell TD. Low Birthweight and Respiratory Disease in Adulthood: A Population-Based Case-Control Study. *Am J Respir Crit Care Med* 2009;180:176-80
3. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007;357:1946-1955.
4. Narang I, Baraldi E, Silverman M, Bush A. Airway function measurements and the long-term follow-up of survivors of preterm birth with and without chronic lung disease. *Pediatr Pulmonol* 2006;41:497-508.
5. Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. *Am J Respir Crit Care Med* 2001;163:1693-1722.
6. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;35:1175-1179.
7. Baraldi E, Azzolin NM, Zanconato S, Dario C, Zacchello F. Corticosteroids decrease exhaled nitric oxide in children with acute asthma. *J Pediatr* 1997;131:381-385.
8. 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.
9. 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.

- 1  
2  
3 10. Paredi P, Kharitonov SA, Barnes PJ. Correlation of exhaled breath temperature with  
4  
5 bronchial blood flow in asthma. *Respir Res* 2005 ;6:15.  
6  
7
- 8 11. Pifferi M, Ragazzo V, Previti A, Pioggia G, Ferro M, Macchia P, Piacentini GL,  
9  
10 Boner AL. Exhaled air temperature in asthmatic children: a mathematical  
11  
12 evaluation. *Pediatr Allergy Immunol* 2009;20:164-171.  
13  
14
- 15 12. Global Strategy for Asthma Management and Prevention, Global Initiative for  
16  
17 Asthma (GINA) 2008. Available from: <http://www.ginasthma.org>.  
18  
19
- 20 13. Piacentini GL, Peroni D, Crestani E, Zardini F, Bodini A, Costella S, Boner AL.  
21  
22 Exhaled air temperature in asthma: methods and relationship with markers of  
23  
24 disease. *Clin Exp Allergy* 2007;37:415-419  
25  
26
- 27 14. Baraldi E, de Jongste JC; European Respiratory Society; American Thoracic  
28  
29 Society. Measurement of exhaled nitric oxide in children, 2001. *Eur Respir J*  
30  
31 2002;20:223-237.  
32  
33
- 34 15. Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of  
35  
36 spirometry. *Eur Respir J* 2005 ; 26:319-338.  
37  
38
- 39 16. Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory  
40  
41 health in prematurely born preschool children with and without bronchopulmonary  
42  
43 dysplasia. *J Pediatr* 2007;150:256-261.  
44  
45
- 46 17. Allen J, Zwerdling R, Ehrenkranz R, et al. Statement on the care of the child with  
47  
48 chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med*  
49  
50 2003;168:356-396  
51  
52
- 53 18. Bhandari A, Bhandari V. Pitfalls, problems, and progress in bronchopulmonary  
54  
55 dysplasia. *Pediatrics* 2009;123:1562-1573  
56  
57
- 58 19. Baraldi E, Bonetto G, Zacchello F, Filippone M. Low exhaled nitric oxide in school-  
59  
60 age children with bronchopulmonary dysplasia and airflow limitation. *Am J Respir  
Crit Care Med* 2005;171:68-72.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

20. Piacentini GL, Bodini A, Peroni D, Ressa M, Costella S, Boner AL. Exhaled air temperature and eosinophil airway inflammation in allergic asthmatic children. *J Allergy Clin Immunol* 2004;114:202-204.

21. Thébaud B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit Care Med* 2007;175:978-985.

22. Coalson JJ. Pathology of bronchopulmonary dysplasia. *Semin Perinatol* 2006;30:179-184.

23. Abman SH. The dysmorphic pulmonary circulation in bronchopulmonary dysplasia: a growing story. *Am J Respir Crit Care Med* 2008;178:114-115

24. Filippone M, Sartor M, Zacchello F, Baraldi E. Flow limitation in infants with bronchopulmonary dysplasia and respiratory function at school age. *Lancet* 2003;361:753-754.

25. Tiddens HA, Hofhuis W, Casotti V, Hop WC, Hulsmann AR, de Jongste JC. Airway dimensions in bronchopulmonary dysplasia: implications for airflow obstruction. *Pediatr Pulmonol* 2008;43:1206-13.

26. Jacob SV, Coates AL, Lands LC, MacNeish CF, Riley SP, Hornby L, Outerbridge EW, Davis GM, Williams RL. Long-term pulmonary sequelae of severe bronchopulmonary dysplasia. *J Pediatr* 1998;133:193-200.

27. Gross SJ, Iannuzzi DM, Kveselis DA, Anbar RD. Effect of preterm birth on pulmonary function at school age: a prospective controlled study. *J Pediatr* 1998;133:188-192.

~~Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. *Pediatrics* 2006;118:108-113.~~

1  
2  
3 Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J  
4  
5  
6 1977;1:1645-1648.  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

**FIGURE LEGENDS**

**Figure 1.** Panel A shows PLET values in the 3 groups; panel B shows FE<sub>NO</sub> values in the 3 groups; panel C shows FVC values in the 3 groups; panel D shows FEV1 values in the 3 groups. \*\*p<0.001 and \*p<0.01 vs healthy controls; #p<0.05 and §p<0.01 vs asthmatic subjects □□ p<0.001 vs BPD survivors

**Figure 2.** Correlation between FE<sub>NO</sub> values and PLET values in BPD, asthmatic and healthy subjects (R=0.42 p=0.004).

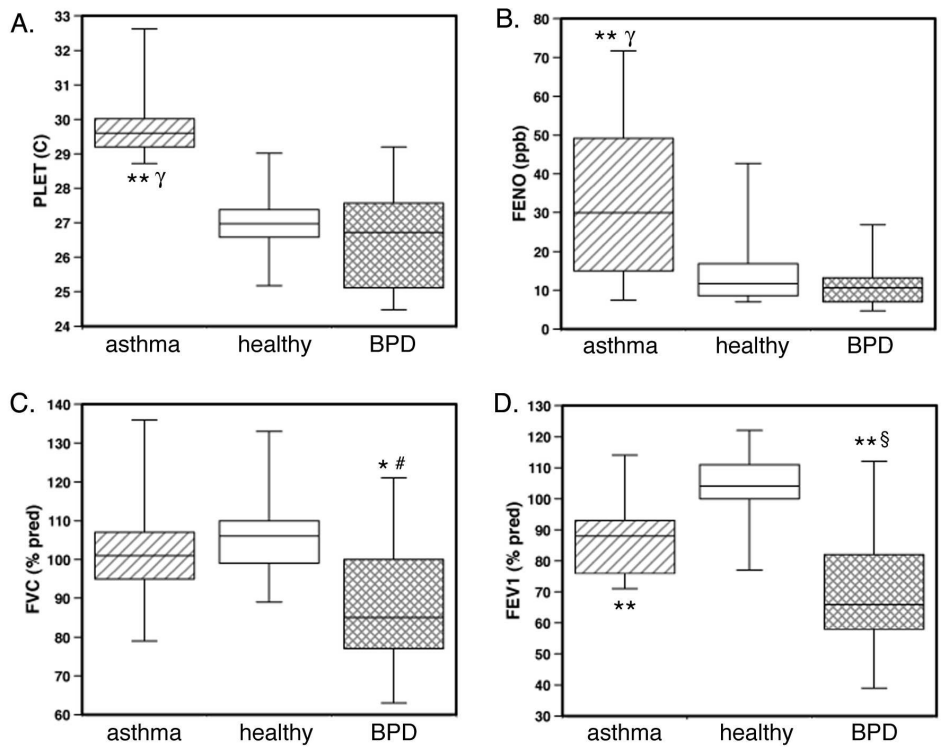
For Peer Review

	Healthy	Asthma	BPD
Number (males)	17 (11)	17 (10)	17 (7)
Age (y)	14.4 (1.8)	13.3 (2.1)	14.5 (2.0)
Height (cm)	163.6 (7.5)	159.5 (9.1)	161.5 (11)
Weight (Kg)	56.5 (9.4)	57.9 (12.9)	53.9 (12.2)
FVC (%pred)	106 [99-110]	101 [95-107]	85 [77-100] <sup>#</sup>
FEV <sub>1</sub> (%pred)	104 [100-111]	88 [76-93] <sup>**</sup>	66 [58-82] <sup>**§</sup>
FEF <sub>25-75</sub> (%pred)	121 [107-133]	75 [57-87] <sup>**</sup>	46 [40-67] <sup>###</sup>
FEV <sub>1</sub> /FVC	91 [88-93]	78 [76-84] <sup>**</sup>	72 [67-80] <sup>**</sup>

**Table.** Demographic characteristic and lung function measures of study subjects. Anthropometric data are expressed as mean (SD). Spirometric data are expressed as median and IQR. <sup>\*\*</sup>p<0.001 and <sup>\*</sup>p<0.01 vs healthy controls; <sup>#</sup>p<0.05 and <sup>§</sup>p<0.01 vs asthmatic subjects.



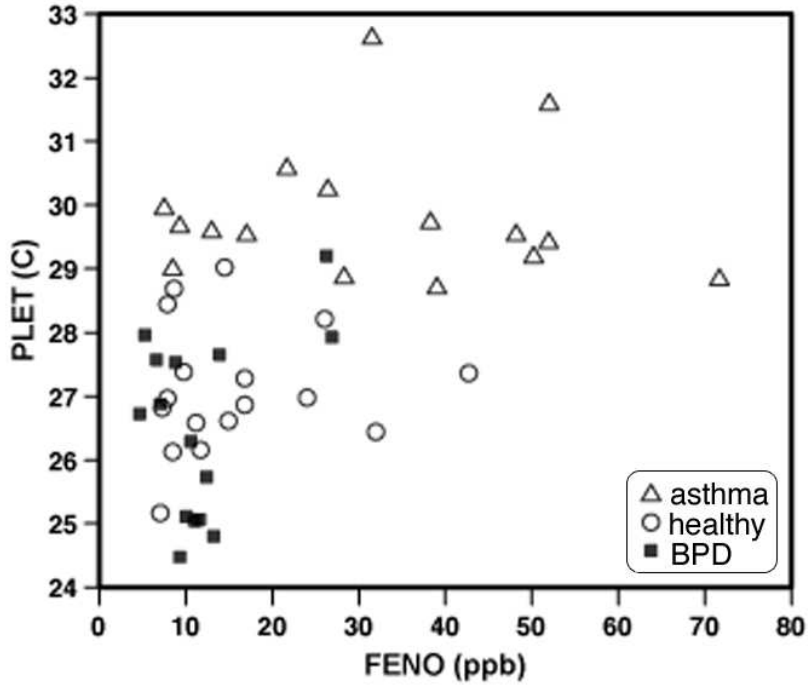
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



160x123mm (300 x 300 DPI)

review

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



70x53mm (300 x 300 DPI)

Review