

Exhaled Breath Temperature and Exercise-Induced Bronchoconstriction in Asthmatic Children

Diego G. Peroni, MD, Iolanda Chinellato, MD, Michele Piazza, MD, Federica Zardini, MD, Alessandro Bodini, MD, Francesca Olivieri, MD, Attilio L. Boner, MD, and Giorgio L. Piacentini, MD*

Summary. It has been hypothesized that exhaled breath temperature (EBT) is related to the degree of airway inflammation/remodeling in asthma. The purpose of this study was to evaluate the relationship between the level of airway response to exercise and EBT in a group of controlled or partly controlled asthmatic children. Fifty asthmatic children underwent measurements of EBT before and after a standardized exercise test. EBT was 32.92 ± 1.13 and $33.35 \pm 0.95^\circ\text{C}$ before and after exercise, respectively ($P < 0.001$). The % decrease in FEV_1 was significantly correlated with the increase in EBT ($r = 0.44$, $P = 0.0013$), being $r = 0.49$ ($P < 0.005$) in the children who were not receiving regular inhaled corticosteroids (ICS) and 0.37 (n.s.) in those who were. This study further supports the hypothesis that EBT can be considered a potential composite tool for monitoring asthma. **Pediatr Pulmonol.**

© 2011 Wiley-Liss, Inc.

Key words: exhaled breath temperature; exercise-induced bronchoconstriction; asthma.

Funding source: none reported

INTRODUCTION

Asthma is characterized by airway inflammation and remodeling of the airway walls, both of which contribute to the pathology of the disease.¹

In recent years, it has been hypothesized that the level of exhaled breath temperature (EBT) is related to the degree of airway inflammation^{2–6} as well as to vascular⁶ and fibrous remodeling⁷ in asthma.

Exercise-induced bronchoconstriction is observed in the majority of asthmatic children⁸ and, though its mechanism is not yet fully elucidated, an interaction between inflammatory cells, their released mediators, and local vascular response has been hypothesized.⁹

The vascular dilation which is observed in response of exercise-induced bronchoprovocation, possibly along with the increased activity of the inflammatory cells in the bronchial wall,^{2–6} can be hypothesized to be responsible for a more pronounced increase in EBT in the asthmatic patients with a greater degree of response to exercise as compared to less reactive ones.

The scientific purpose of this study was to evaluate whether the level of EBT in asthmatic children is related to the degree of the airway response to exercise with the consequent clinical objective to eventually consider a potential role for EBT as an adjunctive tool for a more comprehensive evaluation of the response to exercise testing.

MATERIALS AND METHODS

Subjects and Study Design

This was a cross-sectional study involving 50 allergic asthmatic children, 33 males and 17 females, aged 6–15 years (10.0 ± 1.8 years). At the time of the study the children were all controlled ($n = 24$) or partially controlled ($n = 26$) according to the GINA definition.¹⁰ Thirty-one were not receiving any regular controller therapy and 19 were treated with low dose inhaled corticosteroids (ICS; 100 mcg of fluticasone). No child receiving long-acting beta-2 agonist (LABA) was admitted to the study and none had been treated with short-acting medication in the 48 hr prior to the measurements.

Department of Paediatrics, University of Verona, Verona, Italy.

*Correspondence to: Giorgio L. Piacentini, MD, Department of Paediatrics, Policlinico GB Rossi, Piazzale L. Scuro, 37134 Verona, Italy.
E-mail: giorgio.piacentini@univr.it

Received 13 April 2011; Accepted 4 August 2011.

DOI 10.1002/ppul.21545
Published online in Wiley Online Library
(wileyonlinelibrary.com).

The children were asked to avoid physical activity and to maintain in a resting position in the morning before the beginning of the experimental procedures, which were always performed between 9:00 a.m. and 1:00 p.m.

Core body temperature and EBT were evaluated immediately before the beginning of a standardized exercise test and 30 min after the running session.

Both parents and children gave informed consent. The study was approved by the Research Ethics Committee of the University of Verona Hospital (ClinicalTrials.gov Identifier: NCT00952835).

Exercise Challenge Test and Lung Function Evaluation

A standardized exercise test protocol was used.^{11,12} Briefly, the children performed baseline spirometry and then ran for 6 min on a treadmill at a speed fast enough to achieve a heart rate of 85% of the maximum predicted value [$220 - \text{age (years)}$]. The laboratory was air-conditioned ($19-21^{\circ}\text{C}$; relative humidity $<50\%$) during all the exercise tests. Nose clips were applied to ensure breathing through the mouth. After the exercise challenge, FEV₁ was measured at 1, 3, 5, 10, 15, 20, and 30 min after completing the running sessions. The severity of EIA was expressed as the maximum percentage decrease after exercise from the baseline values of lung function ($\%\Delta\text{FEV}_1$).

Measurements of forced vital capacity (FVC), the best of three manoeuvres according to ATS criteria,¹³ were recorded using an electronic spirometer (Jaeger, Master Screen IOS, Germany) calibrated before the arrival of each subject with a 3 L syringe (Cardinal Health, Germany 234 GmbH). The FVC manoeuvres were carried out with the child standing and wearing a nose clip.

Body and Exhaled Breath Temperature

Body temperature was measured in the ear with an electronic Genius 2 IR Tympanic Thermometer (Tyco Healthcare Group LP, Mansfield, MA).

EBT was measured with an X-Halo device (Delmedica Investments, Singapore) according to previously validated methods.^{14,15} Briefly, the children were requested to inhale freely through the nose and to exhale into the device at a rate and depth typical of

their normal tidal breathing rhythm. The manoeuvre was continued until the built-in software of the instrument indicated that the measured value was stable, fulfilling the criteria of a previously described mathematical model; the instrument processed an incremental temperature curve in relation to the initial temperature of the air in the thermal chamber of the instrument, and was able to capture the achievement of the temperature plateau with an error $<2\%$.¹⁶ The reproducibility of the EBT measurements performed by X-Halo has been previously demonstrated to have an intraclass correlation coefficient of 0.99.¹⁴

Statistical Analysis

The results are expressed as mean $\pm$ SD. Within-group differences before and after exercise were evaluated using the paired Student's *t*-test. Unpaired comparisons were performed using the unpaired Student's *t*-test. Correlations were calculated using Pearson's correlation test.

RESULTS

Grouping for disease control level according to GINA definition¹⁰ and for treatment resulted in age-matched sub-groups. Lung function values for the sub-groups are reported in Table 1.

The mean $\%\Delta\text{FEV}_1$ after exercise was $6.95 \pm 5.79\%$ of the baseline value, being $4.22 \pm 4.37\%$ for those children who were classified as controlled according to the GINA definition¹⁰ versus $9.47 \pm 5.87\%$ for those who were partly controlled ($P < 0.001$) being $7.07 \pm 5.64\%$ for those children who were not receiving regular ICS treatment and $6.74 \pm 6.19\%$ for those who were (n.s.). Seventeen children had a % fall of baseline FEV₁ ($\%\text{FEV}_1 \geq 10\%$ and $33 < 10\%$).

Body temperature was $36.46 \pm 0.3^{\circ}\text{C}$ before exercise and $36.50 \pm 0.24^{\circ}\text{C}$ 20 min after stopping running with a mean change in body temperature ($\Delta\text{bodyT}^{\circ}$) of 0.04°C ($P < 0.03$). Despite the degree of statistical significance, such a narrow $\Delta\text{bodyT}^{\circ}$ should not be considered clinically relevant, not only for its very small magnitude but also in consideration of the lack of any statistically significant relationship with the increase in EBT (ΔEBT) after exercise test ($r = 0.05$; $P = 0.72$).

EBT was 32.92 ± 1.13 and $33.35 \pm 0.95^{\circ}\text{C}$ before and after exercise, respectively ($P < 0.001$), with an

TABLE 1—Lung Function Parameters in the Different Subgroups

	All patients	Controlled	Partly controlled	<i>P</i> -value	Treated	Untreated	<i>P</i> -value
FVC%	106.6 ± 11.7	106.2 ± 11.6	106.9 ± 12.0	n.s.	105.2 ± 8.2	105.5 ± 10.8	n.s.
FEV ₁ %	103.8 ± 12.0	106.0 ± 1	101.9 ± 11.5	n.s.	105.7 ± 6.8	102.4 ± 14.7	n.s.
FEV ₁ /FVC	99.7 ± 8.0	99.1 ± 8.2	94.6 ± 7.3	0.07	99.8 ± 6.9	94.4 ± 8.1	0.03

increase (Δ EBT) of 0.4°C , which was significantly higher than the value of the increase observed for body temperature ($P < 0.001$). Baseline EBT was $32.85 \pm 1.00^\circ\text{C}$ in ICS-untreated children and $33.05 \pm 1.17^\circ\text{C}$ in ICS-treated children (n.s.). It was $32.87 \pm 1.04^\circ\text{C}$ in children with $\%\Delta\text{FEV}_1 < 10$ and 33.03 ± 1.12 in those with $\%\Delta\text{FEV}_1 \geq 10$ (n.s.).

Δ EBT was $0.27 \pm 0.30^\circ\text{C}$ in children who were classified according to GINA guidelines¹⁰ and $0.56 \pm 0.58^\circ\text{C}$ in the partly controlled ones ($P < 0.05$), whereas, it was $0.49 \pm 0.32^\circ\text{C}$ in children who were not receiving regular ICS treatment and $0.32 \pm 0.37^\circ\text{C}$ in those who were (n.s.). When grouping the children according to the 10% baseline fall after exercise, those with $\%\Delta\text{FEV}_1 < 10$ had Δ EBT of $0.30 \pm 0.34^\circ\text{C}$, whereas, Δ EBT was $0.65 \pm 0.63^\circ\text{C}$ for those with $\%\Delta\text{FEV}_1 \geq 10$ ($P = 0.013$; Fig. 1).

Δ EBT was significantly correlated with ΔFEV_1 ($r = 0.44$, $P = 0.0013$), being $r = 0.49$ ($P < 0.005$) for those children not receiving regular ICS and 0.37 (n.s.) for those who were (Fig. 2).

DISCUSSION

To the best of our knowledge, this is the first study designed to evaluate the relationship between response to a standardized exercise test and levels of EBT in asthmatic children. This model was chosen because inflammation, remodeling, and bronchial hyper-responsiveness are related phenomena in the pathology of asthma.¹ Since all the above-mentioned mechanisms of disease contribute to the response to exercise,^{17–22} such a response could be considered a composite index disease.

With this study model we observed a significant increase in EBT after exercise in a group of allergic asthmatic children, which was significantly greater for

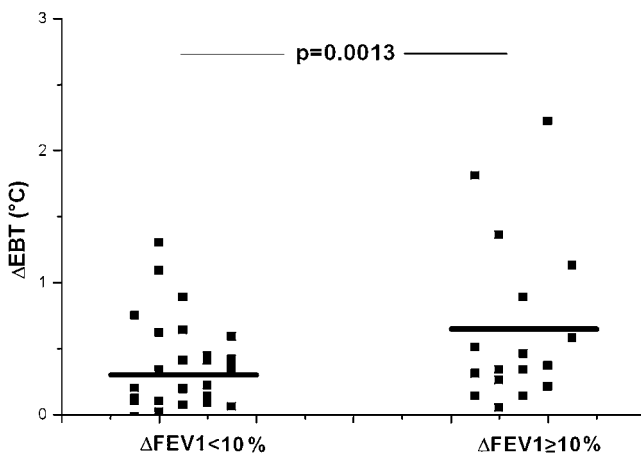


Fig. 1. Individual values for Δ EBT, grouped according to a 10% cut-off of ΔFEV_1 .

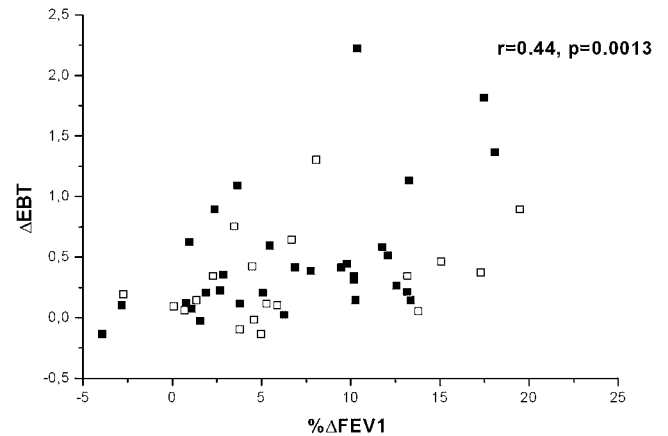


Fig. 2. Relationship between Δ EBT and $\%\Delta\text{FEV}_1$ in the study group. (■, ICS-untreated children; □, ICS-treated children).

partly controlled subjects as compared to controlled ones but was not significantly influenced by grouping the children according to treatment with ICS.

Though the baseline EBT values and the $\%\Delta\text{FEV}_1$ after exercise were not significantly related, the magnitude of the increase in EBT was positively and significantly related to the $\%\Delta\text{FEV}_1$. These relationships are exactly the opposite of those observed in previous studies with a similar experimental design, which measured exhaled nitric oxide instead of EBT.^{19,23–27} In fact, baseline exhaled nitric oxide before exercise has been repeatedly shown to be related to the decrease in FEV_1 after exercise, both in adults^{23–25} and children^{19,26,27}; and a decreased²⁶ or unchanged¹⁹ level of nitric oxide was observed at the end of the exercise test in asthmatic children. Therefore, though the lack of exhaled nitric oxide data for this study does not allow to draw a safe conclusion, it is tempting to speculate that the exhaled nitric oxide and EBT may reflect different effects of exercise on the airway of asthmatic children.

The association between the degree of airway responsiveness to exercise and the baseline levels of exhaled nitric oxide in atopic asthmatic children is consistent with the hypothesis of a relationship between the level of airway inflammation and hyper-responsiveness in this class of patients²⁸ and it is in agreement with the demonstration that the percentage of eosinophils in the airways of asthmatic patients is significantly related to and an independent predictor of EIB severity.¹⁸ EBT and exhaled nitric oxide have previously been reported to be related in asthmatic children, therefore, suggesting a potential role of EBT as a marker of airway inflammation.^{2–6} Nevertheless, the significant relationships observed in the present study between Δ EBT and $\%\Delta\text{FEV}_1$, but not between baseline EBT and the response to exercise, support the idea that EBT could represent a composite indicator of disease in asthma,

including airway vascular remodeling, rather than just be a marker of airway inflammation. This hypothesis is in keeping with the conclusion of a previous study by Paredi et al.⁶ who suggested that EBT, being related to bronchial blood flow, could possibly indicate vascular remodeling in asthma. The rationale for this hypothesis is based on the knowledge that microvascular proliferation at the site of the bronchial mucosa is one of the key features of airway remodeling in asthma, which is related to the degree of severity,²⁹ and that it can be partially responsive to treatment with ICS.^{30,31}

Deeper insight into the possible mechanisms may come from a body of previous studies relating exercise-induced asthma and vascular modifications at the site of the bronchial wall in asthma. A study by Kanazawa et al.³² showed that vascular endothelial growth factor (VEGF) was significantly correlated with the maximal % fall in FEV₁ induced by exercise and with airway vascular permeability, thus confirming a relevant role of vasculature in the pathogenesis of exercise-induced bronchoconstriction.

The same group, in a further study, demonstrated that the severity of exercise-induced bronchoconstriction and the vascular regulatory factor angiopoietin-2 are significantly related in asthmatic patients.⁹ That observation is consistent with the demonstration that angiopoietin-2 is capable of inducing increased vascular leakage,³³ which is not prevented by anti-inflammatory treatment with ICS.³⁴

Furthermore, extremely high pulmonary blood flow has recently been shown to be capable of inducing airway hyper-responsiveness, especially when it is accompanied by an increase in capillary pressure.³⁵ The authors of that study³⁵ suggest that the combination of these phenomena, that is, when they happen simultaneously, can be particularly relevant in exercise testing and exercise-induced asthma.³¹

In a wider perspective, a further link between vascularity and airway remodeling in asthma comes from the observation that VEGF levels are related not only to proliferation of blood vessels but also to fibrosis of the bronchial wall,³⁶ and that it can modulate matrix metalloproteinase-9 (MMP-9) expression in asthma.³⁷ In this regard, EBT was observed to be related to MMP-9 in asthmatic children.⁷

Therefore, though the complex interactions between airway inflammation and remodeling in asthma are largely unknown, it is clear that vascular alterations, both functional, such as the level of bronchial vascular reactivity, permeability and leakage, and anatomic, including the angiogenetic phase of remodeling and its interactions with subepithelial fibrosis, are pivotal characteristics of the disease.³⁸

In conclusion, the data from the present study further support the hypothesis that EBT can be considered a

potential composite research tool for asthma investigation and warrant the necessity for deeper insight on basic mechanisms in order to define the clinical benefit of EBT in asthma monitoring.

REFERENCES

1. Vignola AM, Mirabella F, Costanzo G, Di Giorgi R, Gjomarkaj M, Bellia V, Bonsignore G. Airway remodeling in asthma. *Chest* 2003;123:417S–422S.
2. 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.
3. 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.
4. 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.
5. Paredi P, Kharitonov SA, Barnes PJ. Exhaled breath temperature in asthma. *Eur Respir J* 2003;21:195.
6. Paredi P, Kharitonov SA, Barnes PJ. Correlation of exhaled breath temperature with bronchial blood flow in asthma. *Respir Res* 2005;6:15.
7. Piacentini GL, Peroni DG, Bodini A, Corradi M, Boner AL. Exhaled breath temperature as a marker of airway remodelling in asthma: a preliminary study. *Allergy* 2008;63:484–485.
8. Cabral AL, Conceicao GM, Fonseca-Guedes CH, Martins MA. Exercise-induced bronchospasm in children: effects of asthma severity. *Am J Respir Crit Care Med* 1999;159:1819–1823.
9. Kanazawa H, Tochino Y, Asai K. Angiopoietin-2 as a contributing factor of exercise-induced bronchoconstriction in asthmatic patients receiving inhaled corticosteroid therapy. *J Allergy Clin Immunol* 2008;121:390–395.
10. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2009 Available from: www.ginasthma.com.
11. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ. American Thoracic Society: Guidelines for Methacholine and Exercise Challenge Testing. *Am J Respir Crit Care Med* 2000;161:309–329.
12. Sterk PJ, Fabbri LM. Airway responsiveness: standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J* 1993;6:53–83.
13. American Thoracic Society. Standardisation of spirometry: 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–1136.
14. 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.
15. Xepapadaki P, Xatzioannou A, Chatzicharalambous M, Makrinioti H, Papadopoulos NG. Exhaled breath temperature increases during mild exacerbations in children with virus-induced asthma. *Int Arch Allergy Immunol* 2010;153:70–74.
16. Popov TA, Kralimarkova T, Tzachev C, Dimitrov V, Mun KK, Gill J. Exhaled breath temperature measurement made easy. *Pediatr Allergy Immunol* 2009;20:200–201.
17. Anderson SD. Exercise-induced asthma in children: a marker of airway inflammation. *Med J Aust* 2002;177:S61–S63.
18. Duong M, Subbarao P, Adelroth E, Obminski G, Strinich T, Inman M, Pedersen S, O'Byrne PM. Sputum eosinophils and

- the response of exercise-induced bronchoconstriction to corticosteroid in asthma. *Chest* 2008;133:404–411.
19. Scollo M, Zanconato S, Ongaro R, Zaramella C, Zacchello F, Baraldi E. Exhaled nitric oxide and exercise-induced bronchoconstriction in asthmatic children. *Am J Respir Crit Care Med* 2000;161:1047–1050.
 20. McFadden ER Jr. Hypothesis: exercise-induced asthma as a vascular phenomenon. *Lancet* 1990;335:880–882.
 21. McFadden ER Jr, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994;330:1362–1367.
 22. Anderson SD. Provocative challenges to help diagnose and monitor asthma: exercise, methacholine, adenosine, and mannitol. *Curr Opin Pulm Med* 2008;14:39–45.
 23. El Halawani S, Ly N, Mahon R, Amundson D. Exhaled nitric oxide as a predictor of exercise-induced bronchoconstriction. *Chest* 2003;124:639–643.
 24. Berkman N, Avital A, Breuer R, Bardach E, Springer C, Godfrey S. Exhaled nitric oxide in the diagnosis of asthma: comparison with bronchial provocation tests. *Thorax* 2005;60:383–388.
 25. Rouhos A, Ekroos H, Karjalainen J, Sarna S, Sovijarvi AR. Exhaled nitric oxide and exercise induced bronchoconstriction in young male conscripts: association only in atopics. *Allergy* 2005;60:1493–1498.
 26. Terada A, Fujisawa T, Togashi K, Miyazaki T, Katsumata H, Atsuta J, Iguchi K, Kamiya H, Togari H. Exhaled nitric oxide decreases during exercise-induced bronchoconstriction in children with asthma. *Am J Respir Crit Care Med* 2001;164:1879–1884.
 27. Buchvald F, Hermanssen M, Nielsen KG, Bisgaard H. Exhaled nitric oxide predicts exercise-induced bronchoconstriction in asthmatic children. *Chest* 2005;128:1964–1967.
 28. Malmberg LP, Pelkonen AS, Mattila PS, Hammarén-Malmi S, Mäkelä MJ. Exhaled nitric oxide and exercise-induced bronchoconstriction in young wheezy children—interactions with atopy. *Pediatr Allergy Immunol* 2009;20:673–678.
 29. Salvato G. Quantitative and morphological analysis of the vascular bed in bronchial biopsy specimens from asthmatic and non-asthmatic subjects. *Thorax* 2001;56:902–906.
 30. Hoshino M, Takahashi M, Takai Y, Sim J, Aoike N. Clin Inhaled corticosteroids decrease vascularity of the bronchial mucosa in patients with asthma. *Exp Allergy* 2001;31:722–730.
 31. Feltis BN, Wignarajah D, Reid DW, Ward C, Harding R, Walters EH. Effects of inhaled fluticasone on angiogenesis and vascular endothelial growth factor in asthma. *Thorax* 2007;62:314–319.
 32. Kanazawa H, Hirata K, Yoshikawa J. Involvement of vascular endothelial growth factor in exercise induced bronchoconstriction in asthmatic patients. *Thorax* 2002;57:885–888.
 33. Rudolfsson SH, Johansson A, Franckl L, Wikstrom P, Bergh A. Localized expression of angiopoietin 1 and 2 may explain unique characteristics of the rat testicular microvasculature. *Biol Reprod* 2003;69:1231–1237.
 34. Nomura S, Kanazawa H, Hirata K, Iwao H, Yoshikawa J. Relationship between vascular endothelial growth factor and angiopoietin-2 in asthmatics before and after inhaled beclomethasone therapy. *J Asthma* 2005;42:141–146.
 35. Peták F, Janosi TZ, Myers C, Fontao F, Habre W. Impact of elevated pulmonary blood flow and capillary pressure on lung responsiveness. *J Appl Physiol* 2009;107:780–786.
 36. Chetta A, Zanini A, Foresiz A, D'Ippolito R, Tipa A, Castagnaro A, Baraldo S, Neri M, Saetta M, Olivieri D. Vascular endothelial growth factor up-regulation and bronchial wall remodelling in asthma. *Clin Exp Allergy* 2005;35:1437–1442.
 37. Lee KS, Min KH, Kim SR, Park SJ, Park HS, Jin GY, Lee YC. Vascular endothelial growth factor modulates matrix metalloproteinase-9 expression in asthma. *Am J Respir Crit Care Med* 2006;174:161–170.
 38. Bailey SR, Boustany S, Burgess JK, Hirst SJ, Sharma HS, Simcock DE, Suravaram PR, Weckmann M. Airway vascular reactivity and vascularisation in human chronic airway disease. *Pulm Pharmacol Ther* 2009;22:417–425.