Differences in asthma control and lung function in relation to allergic status

Kuo, Chris; Lipworth, Brian

Published in:
European Respiratory Journal

DOI:
10.1183/13993003.02102-2018

Publication date:
2019

Document Version
Peer reviewed version

EUROPEAN RESPIRATORY journal
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

Differences in asthma control and lung function in relation to allergic status

Journal:	*European Respiratory Journal*
Manuscript ID	ERJ-02102-2018.R1
Manuscript Type:	Research Letter
Date Submitted by the Author:	14-Feb-2019
Complete List of Authors:	Kuo, Chris RuiWen; University of Dundee, Scottish Centre For Respiratory Research Lipworth, Brian; University of Dundee, Scottish Centre For Respiratory Research
Key Words:	asthma, asthma control, type-2 inflammation, Spirometry, impulse oscillometry, allergic asthma
Abstract:	

Title page

Differences in asthma control and lung function in relation to allergic status

Chris RuiWen Kuo MB ChB, Brian Lipworth MD

Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee, DD19SY
Scotland, UK

Correspondence:
Professor Brian Lipworth
Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee, DD19SY
Scotland, UK
Office: +44 1382 383188
Fax: +44 (0)1382 383259
b.j.lipworth@dundee.ac.uk

Take-home message

Our study showed for the first time that non-allergic asthma patients have worse asthma control and lung function in association with lower FeNO.

To the Editor:

Allergic asthma is characterised by the presence of circulating specific immunoglobulin E (IgE) or positive skin prick test (SPT) to common aeroallergen. Type-2 inflammatory (T2) cytokines stimulates IgE synthesis in response to aeroallergen, resulting in chronic eosinophilic (Eos) airway mucosal inflammation.

Non-allergic asthma is defined by a negative SPT and is more typically of later onset with female predominance [1]. While the inflammation in allergic asthma is driven by external allergen, there is no identifiable allergen in non-allergic asthma where the mechanisms of airway inflammation remains unclear.

To our knowledge, presently there are no studies looking at T2 biomarkers as fractional exhaled nitric oxide (FeNO) and Eos, or small airway function as impulse oscillometry (IOS), comparing between allergic and non-allergic asthma. IOS has been utilised to identify small airway dysfunction (SAD) defined by raised peripheral airway resistance which is the difference between resistance at 5 Hz and 20 Hz (R5-R20) and the area under the reactance curve (AX) which reflects the peripheral lung compliance. Indeed the SAD phenotype is related to worse asthma control [2].

We therefore wished to see if there were differences in asthma control (as ACQ), lung function (as spirometry and IOS) and T2 biomarkers (as FeNO and blood Eos) in relation to allergic status in patients with persistent asthma. Retrospectively, we evaluated a cohort of 56 serial patients with persistent asthma who attended our research unit for screening into clinical trials. All asthmatic subjects included were receiving inhaled corticosteroids (ICS) at the time of the visit. Allergy was defined as positive SPT to at least one common aeroallergen. IOS (Jaeger Masterscreen, Hochberg, Germany) and spirometry (Micromedical, Chatham, United Kingdom) were performed in triplicate according to European Respiratory Society guidelines. Caldicott guardian approval was obtained to allow access to the patient identifiable National Health Service data on blood Eos, and all patients consented for their screening data to be accessed.

We analysed the values for asthma control questionnaire (ACQ-6), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), forced expiratory flow at 25-75% of FVC (FEF25-75), IOS (R5, R5-R20, AX), FeNO and Eos. Comparisons for each outcome were made by

unpaired Student's *t* test using Bonferonni corrections to avoid confounding the overall alpha error which was set at 0.05 (2-tailed).

Overall mean age was 51 years, 33 females, mean FEV1 2.65L, mean ACQ score of 1.5, and mean ICS dose (beclomethasone equivalent) of 700ug. 28 subjects were identified with either allergic or non-allergic asthma. Median number of positive SPT in allergic asthma was 2 (interquartile range 2-4) aeroallergens in the allergic group and none in the non-allergic group.

The characteristics of the study subjects and significant comparisons are summarised in Table 1. Patients with allergy had a lower body mass index (BMI) (P=0.01) and were younger (P=0.005). In allergic asthma, the FeNO was significantly higher than in non-allergic asthma, while after Bonferroni correction there was a non-significant numerical difference in Eos amounting to 130 cells/ul. In terms of lung function tests, spirometry for FEV1 and FVC in litres but not FEF25-75 and all IOS measurements were significantly worse comparing non allergic to allergic asthma. FEV1 and FVC as % predicted were not significant with mean values of 91% vs 90% (P=0.72) and 106% vs 103% (P=0.45) comparing allergic and non-allergic asthma respectively. ACQ was also significantly worse in non-allergic asthma.

Our results showed that ACQ, which is a strong predictor of future exacerbations [3], was worse in the non-allergic group with mean difference exceeding minimal clinically important difference (MCID) of 0.5 [4]. Furthermore, the mean difference in FEV1 also exceeded the MCID of 230ml [5].

As expected, the FeNO and Eos levels in allergic asthma were higher reflecting the underlying type 2 inflammatory cytokines. One might perhaps expect lung function to be worse in the presence of high T2 biomarkers in conjunction with the underlying allergic burden. In converse, our results demonstrated that lung function including the small airways outcomes on IOS were indeed worse in non-allergic asthma. This finding is also consistent with a previous study by Ulrik et al [6] showing that the rate of decline in FEV1 was greater in patients with allergic asthma than in non-allergic asthma.

As the mean ICS dose in the non-allergic group was approximately 100µg higher than the allergic group, albeit non-significant, we might therefore have expected the allergic group to exhibit poorer outcomes in terms of ACQ or lung function, whereas the opposite was observed. This can be

explained by T2 high asthma being generally more responsive to ICS therapy [7]. For example, Price et al [8] showed that high T2 biomarkers such as FeNO predicts a better ACQ response to ICS, although this study did not differentiate with regards to allergic status. It has also been shown that allergic patients who have high FeNO and blood eosinophils exhibit greater reductions in exacerbations in response to omazilumab [9].

We duly recognise that there were limitations to our study. First our data was retrospective and cross-sectional. Being a cross sectional study we have no measure of inhaler adherence comparing the two groups of patients, which might perhaps account for differences in control. Also we may have been subject to selection bias, given that these were patients who self-selected for inclusion into clinical trials and hence may not be representative of the wider population of asthma patients per se. Our sample size was rather small, although the significant differences we observed in lung function and symptoms were similar to a previous study [6].

In summary, we have shown that non allergic asthma patients have worse asthma control and lung function in association with lower FeNO. Such patients may be more difficult to manage in terms of not having treatable traits directed at allergy, FeNO and eosinophils. Our data emphasises the importance of detailed phenotyping in asthma patients in order to properly characterise allergic status, T2 biomarkers and lung function.

Word count =985

Table 1

	Allergic asthma	Non-allergic asthma	p-values
Age	45 (17)	57 (13)	-
F/M	15/13	18/10	-
BMI	28 (5)	32 (7)	-
ICS (µg)	644 (300)	754 (390)	-
ICS + LABA	64%	68%	-
LAMA	18%	21%	-
LTRA	36%	29%	-
THEO	4%	7%	-
OAH	29%	0%	-
INS	57%	0%	-
ACQ	1.13 (0.86)	1.80 (0.98)	0.009
FEV_1 (L)	2.92 (0.79)	2.37 (0.67)	0.021
FVC (L)	4.02 (0.77)	3.30 (0.79)	0.003
FEF_{25-75} (L/s)	2.35 (0.11)	1.71 (0.87)	0.060
AX (kPa/L)	0.73 (0.58)	1.46 (1.17)	0.015
R5 (kPa/L.s)	0.42 (0.11)	0.56 (0.17)	0.003
R5-R20 (kPa/L.s)	0.07 (0.06)	0.14 (0.10)	0.009
FeNO (ppb)	55 (28)	37 (28)	0.036
Eos (cells/µL)	413 (198)	283 (251)	0.074

BMI = body mass index, ICS as beclomethasone equivalent dose, LABA = long acting β2 agonist, LAMA = long acting muscarinic antagonist, LTRA = leukotriene receptor antagonist, THEO = theophylline, OAH = oral antihistamine, INS = intranasal steroid. AX= area under the reactance curve, R5=resistance at 5 Hz, R5-R20=difference between resistance at 5Hz and 20Hz. Values are presented as mean and standard deviation (SD). P values are shown as Bonferroni corrected.

References

1. Nieves A, Magnan A, Boniface S, Proudhon H, Lanteaume A, Romanet S, Vervloet D, Godard P. Phenotypes of asthma revisited upon the presence of atopy. *Respiratory medicine* 2005: 99(3): 347-354.
2. Kuo CR, Jabbal S, Lipworth B. Is small airways dysfunction related to asthma control and type 2 inflammation? *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2018.
3. Meltzer EO, Busse WW, Wenzel SE, Belozeroff V, Weng HH, Feng J, Chon Y, Chiou CF, Globe D, Lin SL. Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation. *The Journal of allergy and clinical immunology* 2011: 127(1): 167-172.
4. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respiratory medicine* 2005: 99(5): 553-558.
5. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *The European respiratory journal* 1999: 14(1): 23-27.
6. Ulrik CS, Backer V, Dirksen A. A 10 year follow up of 180 adults with bronchial asthma: factors important for the decline in lung function. *Thorax* 1992: 47(1): 14-18.
7. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, Fahy JV. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *American journal of respiratory and critical care medicine* 2009: 180(5): 388-395.
8. Price DB, Buhl R, Chan A, Freeman D, Gardener E, Godley C, Gruffydd-Jones K, McGarvey L, Ohta K, Ryan D, Syk J, Tan NC, Tan T, Thomas M, Yang S, Konduru PR, Ngantcha M, d'Alcontres MS, Lapperre TS. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *The Lancet Respiratory medicine* 2018: 6(1): 29-39.
9. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM, Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *American journal of respiratory and critical care medicine* 2013: 187(8): 804-811.