Novel views on endotyping asthma, its remission, and COPD

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Chapter 5

Small airways disease and airway inflammation in asthma remission

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Introduction

Asthma is a chronic disease, characterized by variable airflow obstruction and airway inflammation [1]. To date, there is no cure for this disease. Nevertheless asthma can go into spontaneous remission [2,3], meaning that some asthma patients no longer experience symptoms and do no longer require any asthma medication. These subjects might still have (asymptomatic) bronchial hyperresponsiveness or a sub-normal lung function, and then are considered to be in clinical remission [4]. In fewer cases, asthma patients go into complete remission, which means that they no longer have any pulmonary function impairment or bronchial hyperresponsiveness [2,3].

Although asthma affects the entire bronchial tree, small airways - defined as those with an internal diameter of <2 mm - are thought to be a major site of pathology in asthma [6]. The small airways comprise 90% of the total airway volume and significantly contribute to total airway resistance in patients with obstructive pulmonary disease [7,8]. Previous studies have investigated lung function and airway inflammation in asthma remission, but whether and to what extent small airways disease is still present in clinical and complete remission is yet unknown.

The aim of the current study was to more closely investigate the phenotypes of clinical and complete asthma remission. To this end, we extensively characterized subjects with complete and clinical asthma remission and compared them to both patients with asthma and healthy controls. We assessed parameters of large and small airways function next to the presence and extent of markers for Th2 inflammation in blood, sputum and bronchial biopsies.

Methods

The local ethics committee approved the study protocol and all subjects gave their written informed consent (NL53173.042.15, Groningen). Enrolled subjects were aged 40 - 65 years and either never- or ex-smokers with a smoking history <10 pack years. Participants were divided in four groups; subjects with childhood-onset asthma that persisted (PersA; subjects with wheezing and/or asthma attacks, asthma medication use, and a PC_{20} methacholine <8 mg/ml with 120s tidal breathing), individuals who had gone into clinical asthma remission (ClinR; subjects without wheezing/asthma attacks, no use of asthma medication in the last 3 years, with a documented history of asthma according to GINA guidelines, an FEV_1 % predicted <80% and/or PC_{20} methacholine <8 mg/ml), individuals into complete asthma remission (ComR; similar to ClinR, but with an FEV_1 % predicted ≥80%, PC_{20} methacholine ≥8 mg/ml and PC_{20} adenosine 5'-monophosphate (AMP) ≥320 mg/ml), and healthy controls (Ctrl; no history of asthma or use of asthma medication and lung function as in the ComR group). Inhaled corticosteroids were withdrawn six weeks prior to enrollment. Subjects underwent spirometry, body plethysmography, provocation tests, impulse oscillometry (IOS), multiple breath nitrogen wash-out, fractional nitric oxide (FeNO), skin prick tests, and computed tomography (CT)-scans. Parametric Response Mapping was applied on in- and expiratory CT-scans, quantifying functional small airways disease and inferior-to-superior ventilation gradients, both small airways parameters as described previously [10,11].

The four groups were compared using independent sample T-tests for normally distributed data, Mann-Whitney U tests for non-normally distributed data and Fisher's exact tests for categorical variables. Second, a regression analysis was performed to identify and correct for confounders.

Results and discussion

Clinical characteristics of the four groups are presented in table 1. Apart from ComR-subjects being younger than the PersA-patients and healthy controls, no significant differences were seen in demographical characteristics. ComR-subjects had significantly better large and small airways function and less Th2 inflammation as reflected by sputum eosinophils and alveolar nitric oxide than individuals with ClinR. ComR-subjects were similar to healthy controls in this respect, whereas subjects with ClinR were intermediate between PersA and Ctrl, in terms of large and small airways- and inflammatory parameters (table 1). Our results confirm previous studies showing that the asthma remission with absence of bronchial hyperresponsiveness, ComR, is different from ClinR with the level of lung function and Th2 inflammatory markers being reverted towards normal [2,5].

We extend these findings by showing that in addition, complete remission patients have lost all features of small airways disease, both defined by physiological parameters and by in- and expiratory HRCT. Small airway function of complete remission patients is the same as that of healthy controls without a history of asthma. We found that peripheral airways dysfunction as reflected by R_5-R_{20} resistance and AX reactance, was significantly less in asthma remission, both ComR and ClinR, subjects compared to PersA-patients. The Dunedin birth cohort assessed IOS measurements using the forced oscillation technique in healthy individuals, asthmatics and asthma remission subjects at age 38 [12]: the FEV_1 and FEV_1/FVC ratio of the remission subjects were similar to those of healthy controls, suggesting a higher complete remission prevalence. These results are in agreement with ours: asthma remission was associated with a similar R_5-R_{20} resistance and AX reactance to that of healthy controls, whereas persistent asthmatics had increased resistance and reactance. Overall, both associations were stronger in men, and more apparent in childhood-onset asthma, which is in concordance with our data.

We observed that the inferior-to-superior ventilation gradient from HR-CT PRM was positive in persistent asthmatics, while it was negative in all other groups, suggesting that a higher proportion of the asthmatics' ventilation takes place in the superior part of the lung. This is in line with earlier research showing that small airways dysfunction is

lower lobe-predominant in asthmatics [10]. This observation may support the hypothesis that subjects in asthma remission regain their lower lobe ventilation, which might be associated with improvement in symptoms and bronchial hyperresponsiveness. Perhaps the more distal lower lobes are affected most by bronchial hyperresponsiveness due to more central bronchoconstriction. We expect that if the ClinR-group was bigger, the ventilation gradient would also be positive. Future automated CT-scan analyses may incorporate this gradient, illustrating ventilation shifts in disease progression or remission.

Finally, multiple breath nitrogen wash-out, S_{cond} and S_{acin} were significantly higher in persistent asthmatics and ClinR-subjects, compared to healthy subjects and individuals who were into ComR. There were no studies investigating the nitrogen washout parameters in adult subjects in remission, but Steinbacher *et al.* did measure S_{cond} and S_{acin} in children who were in remission for more than one year and either normoresponsive or hyperresponsive to cold dry air challenge during the study [13]. In that study, hyperresponsive children with asthma remission showed a significant increase and decrease in S_{cond} after cold dry air challenge and salbutamol inhalation, respectively. This indicates that small airways dysfunction may still be present in asthma remission subjects that still react to exogenous triggers.

Our study provides evidence that subjects in clinical but not complete asthma remission still have a degree of small airways disease and presence of inflammatory markers. Second, subjects in complete remission are very similar to healthy subjects. Thus, we propose that in order to elucidate the pathophysiology of asthma remission, future studies should focus on the biological pathways responsible for the induction of complete asthma remission. Further work is needed to establish histological differences in airway wall remodeling and inflammatory parameters in complete remission, supplemented by single-cell RNA sequencing [14]. We believe this research in subjects in complete remission to be a promising route of research for elucidating new pathways and perhaps new treatments.

Table 1: clinical features of healthy controls, complete remission, clinical remission, and persistent asthmatic subjects

	Healthy controls (Ctrl, n = 22)	Complete remission (ComR, n = 14)	Clinical remission (ClinR, n = 17)	Persistent asthma (PersA, n = 24)
Demographics				
Sex, male (n, %)	13 (59.1%)	10 (71.4%)	10 (58.8%)	15 (65.2%)
Age (years) [B,E]	57 [51 – 61]	48 [44 – 56]	52 [46 – 58]	58 [49 – 63]
Never/past-smoker ratio (n, %)	8 (63.3%)	12 (85.7%)	15 (88.2%)	20 (87.0%)
Pack years (min-max) [A]	0 [0 – 5]	0 [0 – 6]	0 [0 – 1]	0 [0 – 2]
Age of symptom onset (years)	NA	4 [2 – 5]	5 [0 – 7]	5 [4 – 9]
Asthma-free years [#]	NA	30 [12 – 33]	15 [8 – 33]	NA
BMI (kg/m^2)	24.3 [22.5 – 28.1]	25.3 [22.5 – 27.8]	25.3 [22.8 – 28.4]	26.0 [23.7 – 30.8]
Large airways parameters				
FEV_1 % predicted (%) [A,B*,D]	113.4 (±10.9)	108.4 (±9.1)	85.1 (±22.4)	83.6 (±14.4)
FEV_1/FVC ratio (%) [A,B*,D]	79.5 (±5.4)	78.3 (±5.3)	67.0 (±8.3)	66.7 (±9.3)
Reversibility after salbutamol 400µg (%) [A,B*,D]	2.4 [0.9 – 5.0]	3.4 [1.8 – 5.3]	7.9 [5.0 – 13.1]	6.5 [3.2 – 14.0]
PC_{20} methacholine (mg/ml)	>9.8	>9.8	1.1 [0.3 – 3.4]	0.7 [0.3 – 2.6]
PC_{20} adenosine 5'-monophosphate (mg/ml)	>320	>320	16.4 [2.2 – 65.9]	1.3 [4.0 – 27.4]
Small airways parameters				
$FEF_{25-75\%}$ % predicted (%) [A,B*,D]	79.6 (±19.9)	77.4 (±14.5)	46.5 (±18.0)	42.5 (±17.6)
RV/TLC ratio (%) [A,B*,C]	29.7 (±4.8)	27.6 (±4.9)	31.5 (±6.7)	37.1 (±7.0)
Exhaled particle mass (ng/L) [A,B*]	5.7 [3.0 – 9.6]	4.9 [2.9 – 6.3]	3.1 [0.7 – 5.4]	3.2 [0.6 – 4.3]
IOS R_5-R_{20} resistance (Kpa x s x L^{-1}) [A,B*]	0.02 [-0.01 – 0.05]	0.02 [-0.04 – 0.05]	0.03 [0.003 – 0.11]	0.08 [0.03 – 0.18]
IOS AX reactance (Kpa/L) [A,B*,C]	0.21 [0.08 – 0.40]	0.20 [0.10 – 0.30]	0.24 [0.14 – 1.00]	0.69 [0.35 – 2.20]
MBNW S_{cond} x VT [A,B,D]	0.01 [0.009 – 0.02]	0.01 [0.007 – 0.03]	0.04 [0.03 – 0.08]	0.04 [0.02 – 0.05]
MBNW S_{acin} x VT [A,B*,D]	0.08 [0.07 – 0.13]	0.08 [0.06 – 0.10]	0.14 [0.11 – 0.17]	0.13 [0.11 – 0.19]
Alveolar FeNO (ppb) [B,D]	2.7 [1.7 – 9.5]	2.6 [0.4 – 5.1]	5.8 [3.9 – 10.4]	4.1 [3.1 – 8.1]
TH2 markers				
FeNO at 50ml/s (ppb) [B]	20.4 [13.5 – 26.7]	18.2 [13.0 – 23.9]	21.5 [16.3 – 41.2]	32.9 [17.0 – 48.7]
Blood eosinophils (10^9/L) [A,C]	0.12 [0.09 – 0.16]	0.20 [0.15 – 0.24]	0.15 [0.11 – 0.26]	0.23 [0.16 – 0.42]
Blood eosinophils >0.3 x 10^9/L (n, %) [A]	1 (4.5%)	2 (14.3%)	3 (17.6%)	8 (33.3%)
Sputum eosinophils (%) [A,B]	0.5 [0.2 – 1.0]	0.2 [0.0 – 0.7]	0.8 [0.3 – 9.0]	3.0 [1.0 – 9.2]
Sputum eosinophils >3% (n, %) [A,D]	0 (0.0%)	0 (0.0%)	4 (80.0%)	6 (50.0%)
Atopy parameters				
Self-reported allergic symptoms (n, %) [A]	2 (9.1%)	5 (38.5%)	10 (58.8%)	15 (62.5%)
Inhalation/total IgE ratio (%) [A,B,D]	0.4 [0.1 – 3.4]	1.7 [0.2 – 18.8]	15.0 [5.4 – 22.0]	13.0 [2.0 – 32.8]
Any skin prick test positive (n, %) [A,D]	8 (38.1%)	7 (50.0%)	16 (100.0%)	17 (77.3%)
HR-CT of the thorax				
PRM functional small airways disease (%)	0.6 [0.3 – 4.5]	0.4 [0.1 – 10.6]	0.6 [0.4 – 20.0]	3.0 [0.7 – 9.7]
PRM interstitial lung density (%) [B]	10.3 [9.5 – 17.4]	8.2 [7.4 – 10.1]	10.6 [8.2 – 13.8]	13.2 [9.9 – 19.0]
PRM inferior-to-superior ventilation (ΔHU) [A,B*]	-2.0 (±2.8)	-2.8 (±3.2)	-0.5 (±2.9)	0.4 [-1.3 – 3.5]

Variables are presented in either mean with standard deviation (± ...), median with interquartile range [... - ...], or number with percentage within group (...%). ***#:*** *years without symptoms of wheeze/asthma attacks and asthma medication use,* ***BMI:*** *body mass index,* ***PC_{20}:*** *dosage of agent that causes a 20% FEV_1 decrease,* ***$FEF_{25-75\%}$:*** *forced expiratory flow at 25% to 75% of forced vital capacity,* ***RV/TLC:*** *residual volume / total lung capacity ratio,* ***IOS:*** *impulse oscillometry* ***MBNW****: multiple breath nitrogen wash-out,* ***S_{cond}****: conductive ventilation heterogeneity,* ***S_{acin}****: acinar ventilation heterogeneity;* ***VT****: tidal volume,* ***FeNO****: fractional nitric oxide,* ***HR-CT:*** *high-resolution computed tomography,* ***PRM****: parametric response mapping,* ***A****: P<0.05 difference between Ctrl and PersA using independent T-, Mann Whitney U-, of Fisher's test,* ***B****: P<0.05 difference between ComR and PersA,* ***B*:*** *<0.05 difference between ComR and Persa after correcting for age,* ***C****: P<0.05 difference between ClinR and PersA,* ***D****: P<0.05 difference between ClinR and ComR,* ***E****: P<0.05 difference between ComR and Ctrl.*

Table 2: significantly different clinical features between complete asthma remission subjects either persistent asthmatics

	ComR *versus* PersA B and P-value	
FEV_1 % predicted (%)	0.02	**<0.001**
FEV_1/FVC ratio (%)	0.03	**0.002**
Reversibility after salbutamol 400µg (%)	-0.02	**0.038**
$FEF_{25-75\%}$ % predicted (%)	0.02	**<0.001**
RV/TLC ratio (%)	-0.04	**0.001**
Exhaled particle mass (ng/L)	0.08	**0.030**
Impulse oscillometry R_5-R_{20} (Kpa x s x L^{-1})	-1.70	**0.037**
Impulse oscillometry AX (Kpa/L)	-0.13	**0.035**
MBNW S_{cond} x VT	-2.59	0.257
MBNW S_{acin} x VT	-2.91	0.060
Blood eosinophils (10^9/L)	-0.97	0.113
Sputum eosinophils (%)	-0.02	0.200
Inhalation/total IgE ratio (%)	-0.01	0.159
PRM interstitial lung density (%)	-0.02	0.066
PRM inferior-to-superior ventilation (ΔHU)	-0.06	**0.036**

Variables are presented B coefficients with P-value, ***$FEF_{25-75\%}$****: forced expiratory flow at 25% to 75% of forced vital capacity,* ***RV/TLC****: residual volume / total lung capacity ratio,* ***MBNW****: multiple breath nitrogen wash-out,* ***S_{cond}****: conductive ventilation heterogeneity,* ***S_{acin}****: acinar ventilation heterogeneity;* ***VT****: tidal volume,* ***PRM****: parametric response mapping.*

References

1 GINA. Pocket Guide For Asthma Management and Prevention. Updated 2019. 2019. www.ginasthma.org

2 Broekema M, Timens W, Vonk JM, *et al.* Persisting remodeling and less airway wall eosinophil activation in complete remission of asthma. Am J Respir Crit Care Med 2011;183:310–6.

3 Carpaij OA, Nieuwenhuis MAE, Koppelman GH, *et al.* Childhood factors associated with complete and clinical asthma remission at 25 and 49 years. Eur Respir J 2017;49:1601974.

4 Carpaij OA, Burgess JK, Kerstjens HAM, *et al.* A review on the pathophysiology of asthma remission. Pharmacol Ther Published Online First: 8 May 2019.

5 Vonk JM, Nieuwenhuis MAE, Dijk FN, *et al.* Novel genes and insights in complete asthma remission. Clin Exp Allergy Published Online First: 22 May 2018.

6 Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. Lancet Respir Med 2014;2:497–506.

7 Postma DS, Brightling C, Baldi S, *et al.* Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med 2019;7:402–16.

8 Bjermer L. The role of small airway disease in asthma. Curr Opin Pulm Med 2014;20:23–30.

9 Broekema M, Volbeda F, Timens W, *et al.* Airway eosinophilia in remission and progression of asthma: Accumulation with a fast decline of FEV1. Respir Med 2010;104:1254–62.

10 Bell AJ, Foy BH, Richardson M, *et al.* Functional Ct Imaging For Identification Of The Spatial Determinants Of Small Airways Disease In Adult Asthma. J Allergy Clin Immunol Published Online First: 22 January 2019.

11 Galbán CJ, Han MK, Boes JL, *et al.* Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. Nat Med 2012;18:1711–5.

12 Robinson PD, King GG, Sears MR, *et al.* Determinants of peripheral airway function in adults with and without asthma. Respirology 2017;22:1110–7.

13 Steinbacher M, Pfleger A, Schwantzer G, *et al.* Small airway function before and after cold dry air challenge in pediatric asthma patients during remission. Pediatr Pulmonol 2017;52:873–9.

14 Vieira Braga FA, Kar G, Berg M, *et al.* A cellular census of human lungs identifies novel cell states in health and in asthma. Nat Med 2019;1.