Longitudinal assessment of loss and gain of lung function in childhood asthma

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Abstract

Background: The Childhood Asthma Management Program study revealed that 25.7% of children with mild to moderate asthma exhibit a loss of lung function. The objective was to assess the trajectories of function by means of serial FEV1 in asthmatic children participating in out-of-hospital follow-up. Methods: A total of 295 children (199 boys) who had undergone at least 10 spirometry tests from the age of 8 were selected from a single-center open cohort. The annualized rate of change (slope) for prebronchodilator FEV1 (percent predicted) was estimated for each participant and three patterns were defined: significantly positive slope, significantly negative slope, and null slope (non-significant P-value in the Pearson test). The standard deviation (SD) of each individual slope was recorded as a variability criterion of FEV1. Results: The median (25th and 75th percentile) age at inclusion and the last visit was 8.5 (8.2, 9.3) and 15.4 (14.8, 16.0) years, respectively. Tracking of function (null slope) was observed in 68.8% of the children, while 27.8% showed a loss of function (negative slope) and 3.4% showed a gain in function (positive slope). The children characterized by loss of function depicted a better initial function and a lower FEV1 variability during their follow-up than children with tracking or gain of lung function. At the last visit, these children were characterized by a lower lung function than children with tracking or gain of lung function. Conclusion: Children with a better initial FEV1 value and less FEV1 variability are more prone to loss of lung function.

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This study has not been founded

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Abstract

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Methods : A total of 295 children (199 boys) who had undergone at least 10 spirometry tests from the age of 8 were selected from a single-center open cohort. The annualized rate of change (slope) for prebronchodilator FEV_1 (percent predicted) was estimated for each participant and three patterns were defined: significantly positive slope, significantly negative slope, and null slope (non-significant P-value in the Pearson test). The standard deviation (SD) of each individual slope was recorded as a variability criterion of FEV_1.

Results : The median (25^{th} and 75^{th} percentile) age at inclusion and the last visit was 8.5 (8.2, 9.3) and 15.4 (14.8, 16.0) years, respectively. Tracking of function (null slope) was observed in 68.8% of the children, while 27.8% showed a loss of function (negative slope) and 3.4% showed a gain in function (positive slope). The children characterized by loss of function depicted a better initial function and a lower FEV_1 variability during their follow-up than children with tracking or gain of lung function. At the last visit, these children were characterized by a lower lung function than children with tracking or gain of lung function.

Conclusion : Children with a better initial FEV_1value and less FEV_1 variability are more prone to loss of lung function.

Introduction

As reported by Martinez,[1] approximately 40% of the deficits in maximal expiratory flow observed at 6 to 7 years of age in children with asthma were present at birth, whereas 60% of the deficits develop during the preschool years.[2] A further decline in FEV_1 occurs during the school years as part of the natural history of asthma.[3] Only one study has demonstrated that asthmatic children can exhibit a loss of lung function during childhood based on spirometry.[4] In this study, a reduction in postbronchodilator FEV_1% predicted was observed in 25.7% of children with mild to moderate asthma who were enrolled in the Childhood Asthma Management Program (CAMP).[4] Factors associated with a reduction in postbronchodilator FEV_1% predicted included a younger age at enrollment, male sex, study site and higher postbronchodilator FEV_1% predicted at baseline. As a consequence, the results of Covar and colleagues should be confirmed (1) using a more common asthma definition criteria, as hyperresponsiveness to methacholine was an inclusion criterion in their study,[4] and (2) in an out-of-hospital series of children that is more representative of childhood asthma than a cohort included in a therapeutic trial involving children with mild to moderate persistent asthma.

The objective of our prospective observational study was to assess whether an abnormal decline in the trajectory of lung function by means of serial FEV_1 monitoring can be identified in asthmatic children participating in out-of-hospital follow-up.

Materials and Methods

Study design

This cohort study complied with STROBE guidelines and with the guidance provided by the editors of respiratory, critical care, and sleep journals.[5]

The La Berma open cohort enrolls asthmatic children since 2009. This open cohort is constituted of 7817 children with asthmatic symptoms (with or without confirmed variable expiratory flow limitation). For this study, selection was made in children with confirmed asthma: suggestive symptoms and (1) a significant bronchodilator response (either sRaw or FEV_1, n=1152) or (2) by an asthma exacerbation diagnosed and

treated in a hospital Emergency Department (n=1295) or (3) both (n=777). Preterm birth (gestational age <37 weeks) was a non inclusion criterion as it is a well-known risk factor for the development of persistent airflow limitation.[6] Only children who had at least 10 pulmonary function tests after 8 years of age were selected to ensure the quality of spirometry, leaving 295 children with confirmed asthma. The characteristics of each visit have been standardized,[7] as described in Table 1.

This cohort was registered to our regulatory agency for electronic data collection (Commission Nationale Informatique et Libertés, no. 1408710). Approval from the Ethics Committee of the French learned Society of Pulmonology (SPLF) was obtained (CEPRO 2009/019). All children and parents were informed of the prospective recording of clinical and physiological data and could request to be exempted from the study in accordance with French law regarding non-interventional research.

Pulmonary function tests

Spirometry (MasterScreen Body; Jaeger, CareFusion, San Diego, CA, USA) was performed without inhaled treatment (bronchodilator or LABA/ICS association) on the day of measurement by the same operator (BM),[7] according to international guidelines.[8] Reference values were those of GLI-2012,[9] as recommended for describing the progression of pulmonary function.[10]

Classification of lung function patterns

The annualized rate of change (slope) for prebronchodilator FEV_1 percent predicted was estimated for each participant using standard least squares linear regression models, as performed by others.[11] Three patterns were defined. A positive slope was defined by a significantly positive value of the slope, whereas a negative slope was defined by a significantly negative value of the slope according to the P-value obtained in the Pearson test. When the P-value was not significant, the slope was considered null. The standard deviation (SD) of each individual slope was recorded as a criterion of FEV_1 variability.

Statistical analyses

The results were expressed as median (25^{th} and 75^{th} percentile) as some indices did not conform to a normal distribution, and the positive slope group was small. Comparisons of continuous variables between the three groups of children were performed using the Kruskal-Wallis test, and subsequent intergroup comparisons were performed using the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. A P-value <0.05 was deemed statistically significant. All statistical analyses were performed with Statview 5.0 software (SAS institute, Cary, NC, USA).

Results

The clinical and functional characteristics of the 295 asthmatic children are presented in Table 1. Three patterns were evident: tracking of lung function (null slope of FEV_1% predicted change over time) in 68.8% of children (95% confidence interval (CI) [63.5%, 74.1%]), loss of lung function (negative slope) in 27.8% (95% CI [22.7%, 32.9%]), and gain in lung function (positive slope) in 3.4% (95% CI [1.3%, 5.5%]).

The children characterized by loss of lung function depicted a better initial lung function (highest z-scores of FEV_1, FVC and FEV_1/FVC) and a lower FEV_1 variability (SD of the slope) during their follow-up than children with tracking or gain of lung function. At the last visit, these children were characterized by a lower lung function (lowest z-scores of FEV_1, FVC and FEV_1/FVC) and lower BMI than children with tracking or gain of lung function. At this last visit, these children had a better level of asthma control than the children with tracking of lung function, while receiving similar asthma treatment.

Overall, the children characterized by a gain in lung function evolved in an opposite way to those losing function. The Figure 1 shows changes in FEV_1% predicted over time in the three different groups based on individual slopes and the Figure 2 shows the relationship between z-score of FEV_1 at inclusion and individual FEV_1 slopes in the three different groups.

Finally, we determined the number of asthmatic children with severe asthma (defined by airflow limitation):

45/295, 15%, 95% CI [11 to 19%], which was more frequent in children with a decline in lung function than in children with tracking of function (see Table 1). As compared to the 250 children without severe asthma, those with severe asthma had a lower initial FEV_1 (87% ±14 versus 95 ±14, p<0.001), a lower initial z-score of FEV_1/FVC (-1.67 ±0.88 versus -1.10 ±0.97, p<0.001) and a higher ICS dose at the last visit (423 µg ±223, n=34 versus 340 ±208, n=141; p=0.0418); the exacerbation frequency of these two groups was not different (p=0.367).

Discussion

The main result of our observationnal study is to confirm the result of the CAMP study showing that about a quarter of asthmatic children participating in out-of-hospital follow-up exhibited loss of lung function during childhood and adolescence.

We have previously shown, in a retrospective study, that a significant increase in prebronchodilator sRaw was observed in 17% of the children (mainly boys with a lower initial and higher final specific resistance) who suffered from persistent asthma.[12] Nevertheless, the effect of lung growth (dysanaptic or isotropic, modifying sRaw via thoracic gas volume) was identified as a potential source of bias. The CAMP study used a predefined criterion of loss of lung function, which was at least 1% loss in postbronchodilator FEV_1% predicted per year.[4] Using a statistical definition of the loss of lung function, we were able to confirm the results of the CAMP study (25.7% versus 27.8%). It should be emphasized that our three groups were differentiated based on prebronchodilator FEV_1 slopes. In most cohorts, the evaluation of longitudinal lung function is based on prebronchodilator values of FEV_1 with bronchodilator withdrawal on the day of testing.[13,14] This may introduce a source of bias as some asthmatic patients may occasionally exhibit some degree of airflow limitation and a positive bronchodilator response. In order to reduce the effect of occasional FEV_1 variability, we calculated slopes using at least 10 spirometry results, as persistent significant bronchodilator response is a rare endotype of asthma (5%).[15] Moreover, Bui and colleagues have recently shown that baseline asthma was associated with accelerated decline in both pre- and post-bronchodilator FEV_1.[16]

The observation that children with better initial lung function at study entry exhibited a loss of lung function is similar to other studies.[4,7,11] Their frequency of severe exacerbation leading to emergency department visit was not different, and they had a better level of control at their last visit, than children with tracking of lung function. Thus, asthma control does not seem to be a risk factor of loss of lung function in our study. Among risk factors of loss of lung function, elevated blood eosinophils have been associated with an accelerated decline in FEV_1 and vital capacity compared to normal blood eosinophils in the younger asthmatic subjects in longitudinal studies.[17] Overall, the inflammatory phenotype in asthma has prognostic relevance since the annual decline in FEV_1 can also be predicted by the bronchial CD8+ cell infiltrate.[18] In our study, sex, age at first symptoms and atopy status were not significantly different in children exhibiting loss of lung function while asthma severity was different, which seems overall consistent with the overview made by Ulrik.[19]

Recently, Denlinger and colleagues evaluated corticosteroid response endotypes as longitudinal predictors of lung decline of adults in the NHLBI Severe Asthma Research Program.[11] The odds ratios of BMI (for 5-unit decrease) and baseline FEV_1% predicted (for a 10-unit increase) for predicting decline were of borderline significance (1.06 [0.95, 1.19] and 1.07 [0.96, 1.19], respectively), which may be consistent with our results. Of note, the effect of BMI in these two studies may seem opposite to the expected effect as overweight has been associated with reduced FEV_1/FVC z-score.[20] Accordingly with our results, Graff and colleagues recently showed that a lower BMI is associated with lung function decline and irreversible airflow obstruction in adult asthma.[21] Overall, why a better initial lung function is a risk factor of subsequent loss of lung function, which has consistently been found, remains unexplained but cannot seem ascribable to regression toward the mean. This phenomenon arises if a sample point of a random variable is extreme, a future point is likely to be closer to the mean or average; thus, in our study the slope criteria were defined a priori and were calculated based on at least 10 measurements.

An original finding of the current study is that less variability in prebronchodilator FEV_1 values over time is associated with loss of lung function. Tantisira and colleagues showed that a single higher bronchodilator

response at inclusion was an independent predictor of higher prebronchodilator FEV_1 after four years in the CAMP study.[22] Thus, occasional FEV_1 variability could be associated with a better prognosis, which may explain that absence of variability is associated with a worst functional prognosis.

The European Respiratory Society /American Thoracic Society guidelines define severe asthma not only as asthma that remains uncontrolled despite aggressive drug therapy, but also one that requires aggressive therapy to prevent from becoming uncontrolled.[23]Airflow limitation (after appropriate bronchodilator withhold FEV_1 <80% predicted, in the face of reduced FEV_1/FVC defined as less than the lower limit of normal) that is one of the four criteria of uncontrolled asthma was quite frequent (15%) and logically more frequent in children with loss of function. Lung function may continue to decline in severe asthmatics despite high-intensity treatment and improved asthma control is not sufficient to prevent such progressive deterioration,[24] as suggested by our results. It highlights that the future risks of severe asthma are poorly recognized by both patients and physicians, may be because patients with loss of function have the best initial lung functions. In the study of McGeachie et al. including 684 study participants of the CAMP trial, (mean age, 26.0±1.8 years), a total of 23% were classified as having reduced growth without an early decline while 26% were classified as having reduced growth and an early decline.[14] Therefore, reduced growth (loss of lung function during childhood) may further affect the prevalence of chronic obstructive pulmonary disease that is an important message. Smoking prevention in these patients is mandatory.

An unexpected finding was the discovery of a small subset (3%) of asthmatic children who exhibited a gain in lung function. This result is in line with individual data of the CAMP study (see appendix of[14]), in which some children clearly exhibited a gain in lung function during childhood or adolescence based on prebronchodilator FEV_1% predicted. This result is also consistent with the pattern of early low, accelerated growth, normal decline (8% of participants) evidenced in the Tasmanian Longitudinal Health Study (16% of participants with ever asthma and 4% with persistent asthma) which modelled lung function trajectories measured at 7, 13, 18, 45, 50 and 53 years based on prebronchodilator FEV_1 z -scores.[25]

Our study has some limitations, such as its monocenter design. The children were in an open cohort; thus, there was a selection bias as asthmatic children who were followed up for years were probably more symptomatic. The percentage of children exhibiting loss of lung function may have been overestimated. Nevertheless, this percentage was similar to that observed in the CAMP study that included mild to moderate persistent asthmatic children, which deserved to be confirmed in an out-of-hospital setting.

In conclusion, we confirm the results of the CAMP study showing that a significant proportion (27.8%) of asthmatic children exhibits a loss of lung function during childhood and adolescence, additionally a small subset of asthmatic children exhibits a gain in lung function.

Author Contributions: Conceptualization: BM and CD2; Formal analysis: PB, CD2; Investigation: BM; Methodology: PB, NB; Project administration: CD2, NB; Supervision: CD2, NB; Validation: BM, CD2; Roles/Writing - original draft: CD2; Writing - review &editing: BM, PB, NB.

Key Message

Only one study has demonstrated that asthmatic children can exhibit a loss of lung function during childhood based on spirometry, in a therapeutic trial (CAMP study). This result deserved to be confirmed in an out-of-hospital setting. We show that tracking of function was observed in 68.8% of the children, while 27.8% showed a loss of function and 3.4% showed a gain in function. We thus confirm the results of the CAMP study.

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Table 1. Characteristics of the 295 asthmatic children according to the three groups of FEV_1 % predicted slope.

Characteristics N (% population)	**Positive slope 10 (3.4)**	**Null slope 203 (68.8)**	**Negative slope 82 (27.8)**	P value	Intergroup comparisons
Sex, male (%)	5 (50) 5 3 0 [0;	135 (67) 89 88	59 (72) 38 38 0	0.3284 0.8767	1,2<3 1,2>3
Atopic	3] 1 1 8 5 4 5.9	1 [0; 4] 22 46	[0; 3] 7 15 60	0.6049 0.3989	
dermatitis, n	[5.0; 6.7] 0.000	135 102 82 6.4	40 32 6.9 [6.1;	0.8442 0.4897	
Early	[0.000; 0.071]	[5.6; 7.2] 0.066	7.6] 0.071	0.4038 0.9752	
wheezing, n	12 [12; 14] 56	[0.000; 0.200]	[0.000; 0.166]	0.9774 0.0098	
Age at first	[49; 65] 25 [16;	12 [11; 14] 55	13 [11; 15] 53	0.5088 0.1240	
symptoms,	31] **+3.58**	[47; 62] 21 [15;	[47; 61] 20 [14;	0.5478 0.4196	
years Atopy	**[+2.17;**	31] **-0.46**	26] **-2.77**	ND <0.0001	
status negative	**+4.52]** 1.05	**[-1.51;**	**[-3.51; -2.11]**		
skin prick	[0.83; 1.51]	**+0.45]** 1.15	0.79 [0.64;		
tests, n		[0.85; 1.52]	0.98]		
one positive prick test, n					
more than one positive prick test, n					
Parental atopy, n					
Parental asthma, n					
Longitudinal PFT characteristics					
Duration of follow-up, years					
ED Hospitalization frequency*					
Number of PFT					
Best sRaw reversibility in the past					
Best FEV_1 reversibility in the past					
FEV_1 slope, % per year					
SD of FEV_1 slope					

Characteristics N (% population)	**Positive slope 10 (3.4)**	**Null slope 203 (68.8)**	**Negative slope 82 (27.8)**	P value	Intergroup comparisons
Spirometry at inclusion	9.3 [8.6; 11.9]	8.5 [8.2; 9.4]	8.4 [8.2; 8.9]	0.0187 0.2506	1>2,3 1<2<3
Age, years	1.50 [1.42;	1.61 [1.41;	1.62 [1.48;	<0.0001	1<2<3 1,2<3
FEV_1, L	1.64] 84 [76;	1.76] 93 [83;	1.78] 99 [90;	<0.0001	1,2<3 1,2<3
FEV_1, %	88] -1.40	102] -0.58	109] -0.09	0.8246 0.0198	1>3
predicted	[-1.98; -1.04]	[-1.42; +0.15]	[-0.83; +0.74]	0.0020 0.0024	
FEV_1, z-score	2.09[1.92; 2.25]	2.04 [1.79;	2.01 [1.83;	0.0240	
FVC, L	-0.30 [-0.87;	2.29] +0.27	2.25] +0.66		
FVC, z-score	+0.28] 0.75	[-0.49; +0.99]	[-0.23; +1.23]		
FEV_1/FVC	[0.71; 0.76]	0.79 [0.73;	0.82 [0.77;		
FEV_1/FVC, z-score	-2.04 [-2.31;	0.84] -1.34	0.87] -1.07		
Obstructive defect, n (%)	-1.65] 7 (70)	[-2.08; -0.76] 82 (40)	[-1.73; -0.28] 24 (29)		
Spirometry at last follow-up	3.82 [3.06;	3.30 [2.77;	2.91 [2.67;	0.0017	1,2>3 1>2>3
FEV_1, L	4.28] 101 [95;	3.75] 91 [84;	3.44] 82 [74;	<0.0001	1>2>3 1,2>3
FEV_1, %	105] +0.06	100] -0.76;	88] -1.46	<0.0001	1,2>3 1,2>3
predicted	[-0.44; +0.40]	-1.38; -0.01]	[-2.14; -1.00]	0.1465 0.0006	1,2<3 2<3
FEV_1, z-score	5.07 [3.59;	4.21 [3.54;	4.00 [3.56;	0.0003 0.0004	
FVC, L	5.38] +0.31	4.88] +0.14	4.47] -0.49	0.0008 0.0089	
FVC, z-score	[-0.10; +0.63]	[-0.59; +0.86]	[-1.11; +0.31]		
FEV_1/FVC	0.82 [0.81;	0.78 [0.73;	0.74 [0.70;		
FEV_1/FVC, z-score	0.83] -0.81	0.84] -1.33	0.80] -1.88		
Obstructive defect[#], n (%)	[-0.96; -0.64] 1	[-1.97; -0.75]	[-2.35; -1.09]		
Severe asthma, (%)[§]	(10) 1 (10)	72 (35) 23 (11)	46 (55) 21 (26)		

Characteristics N (% population)	**Positive slope 10 (3.4)**	**Null slope 203 (68.8)**	**Negative slope 82 (27.8)**	P value	Intergroup comparisons
Clinical characteristics at last follow-up	15.6 [15.3; 17.1] 21.1 [18.8; 23.4] 5 5 400 [325; 620] 3 4 0 [0; 5] 0	15.3 [14.6; 16.0] 20.2 [18.8; 22.0] 80 123 400 [200; 400] 114 94 1 [0; 7] 21	15.5 [14.9; 16.0] 18.9 [17.8; 20.7] 35 47 400 [200; 400] 46 25 0 [0; 3] 4	0.1262 0.0044 0.7290 0.7290 0.4971 0.2631 0.0492 0.0351 0.2010	1,2>3 2>3 2>3
Age, years					
BMI, kg.m^{-2}					
SABA on demand, n					
ICS, n ICS dose, BED µg/day LABA, n Partially or uncontrolled last 3 months, n Days, symptoms within last 3 months Severe exacerbation[$] within last 3 months, n					

*: frequency per year of hospitalization in a hospital Emergency Department (ED) for severe asthmatic exacerbation, calculated since two years of age

#: an obstructive defect is defined by a z-score of $FEV_1/FVC < -1.645$.

BMI denotes body mass index, SABA denotes short-acting beta agonist treatment, ICS denotes inhaled corticosteroid, BED denotes beclomethasone-equivalent daily dose, LABA denotes long-acting beta agonist

[$]: severe exacerbation is defined according to Reddel et al.[26]

[§]: Severe asthma defined by $FEV_1 < 80\%$ predicted and a z-score of $FEV_1/FVC < -1.645$, according to international recommendations[23]

Figure legends

Figure 1. Lung function trajectories of the 295 asthmatic children.

As stated in the Methods, participants were classified into three slope categories, namely loss of function (significant negative slope), gain of lung function (significant positive slope) and null slope (non-significant slope). The lines are the individual FEV_1 % predicted slopes over age (either positive, n=10 or negative, n=82). X axis is the age (8 to 18 years old) and Y axis is FEV_1 % predicted (50 to 130%).

Figure 2. Relationship between z-score of FEV_1at inclusion and individual FEV_1 slopes.

The annualized rate of change (slope) for prebronchodilator FEV_1 percent predicted was estimated for each participant and is described according to the z-score of FEV_1 at inclusion for the three groups of slopes (negative, null or positive). A positive slope was defined by a significantly positive value of the slope, whereas a negative slope was defined by a significantly negative value of the slope according to the P-value obtained in the Pearson test. When the P-value was not significant, the slope was considered null.

A significant linear relationship between FEV_1 at inclusion and the subsequent slope is evidenced using the Pearson test (R= -0.36, p<0.0001).