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Early View

Research letter

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Edouard Dufetelle, Plamen Bokov, Christophe Delclaux, Nicole Beydon

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Should reversibility be assessed in all asthmatic children with normal spirometry?

Edouard Dufetelle[1], Plamen Bokov[2,3,4], Christophe Delclaux[2,3,4], Nicole Beydon[1,5]

[1] APHP, Unité Fonctionnelle de Physiologie-Explorations Fonctionnelles Respiratoires Pédiatrique; Hôpital Armand Trousseau, Paris; France

[2] : AP-HP ; Hôpital Universitaire Robert Debré ; Service de Physiologie Pédiatrique; Paris; France

[3] : INSERM, UMR1141 ; Hôpital Universitaire Robert Debré; Paris; France

[4] : Université Paris Diderot ; Sorbonne Paris Cité ; Faculté de Médecine; Paris; France

[5] : INSERM U938 ; Centre de Recherche Saint Antoine; Paris; France

Correspondance to Dr Nicole Beydon, Unité Fonctionnelle de Physiologie-Explorations Fonctionnelles Respiratoires (EFR), Hôpital Armand-Trousseau 26 Avenue du Docteur Arnold Netter, 75571 Paris Cedex 12, France.

Phone : +33 144 73 63 32, Fax +33 144 73 63 36, E-mail: nicole.beydon@trs.aphp.fr

Take home message: In asthmatic children with normal baseline spirometry, a significant reversibility is detected in only 4.9% of cases

To the editor:

Spirometry is usually normal at baseline in asthmatic children referred for pulmonary function testing (PFTing) [1], still a positive response to bronchodilator can be evidenced in these children [2, 3]. The detection of a significant bronchodilator response (BDR) is not meaningless as it confirms asthma, and independently predicts subsequent level of forced expiratory volume in 1 s (FEV_1) [4], response to inhaled corticosteroids [5], or correlates to increased exhaled NO [6].

The probability of a positive BDR [7] decreases with increasing values of baseline spirometry indices [5] and should be rare in asthmatic children free of acute exacerbation who exhibit a normal baseline spirometry [8]. For practical use, we aimed to determine PF indices thresholds to refute a reversibility test in these children. [7]. We hypothesized that in these specific children, a positive BDR could reveal either a mild central airway obstruction with FEV_1/FVC just above the lower limit of normal (LLN), or a mild presentation of small airway obstructive syndrome defined by a Forced Vital Capacity (FVC) reversibility 10% or greater [7, 9, 10]. According to these hypotheses, positive BDR would be associated with similar Total Lung Capacity (TLC), but increased Residual Volume (RV) to TLC ratio and resistance compared to negative BDR [9].

We retrospectively assessed in asthmatic children 1) the prevalence of positive BDR; 2) sensitivity and specificity of baseline spirometry indices to detect a positive BDR; 3) the complementary information given by independent indices of abnormal PF.

We extracted from the PFT database (declared to the French authority for data protection, CNIL) of Trousseau University Hospital all asthmatic children's files between 2009 and 2017. All children were referred with a medical diagnosis of asthma (in 93.5% of the cases by a paediatric pulmonologist or allergologist of our tertiary hospital) for a first or for a follow-up test. After baseline measurements, children were systematically tested with a bronchodilator (400 µg of salbutamol via a spacer Vortex Pari® Starnberg, Germany), except if a bronchial hyperresponsiveness test was prescribed. All PFT were performed according to the ATS/ERS recommendations (recording of the best of at least two reproducible flow-volume loops, of the median of 5 interrupter resistance (Rint) measurements or of the mean of the median of 3 series of specific airway conductance (sGaw) measurements) [11, 12] and took place at least 6 hours after the last dose of short-acting bronchodilator in children free of acute exacerbation. PFT indices were expressed as z-scores for spirometry (LLN: -1.64), sGaw (LLN: -1.96), and Rint (Upper LN (ULN): +1.96) [8, 12, 13]. In Caucasian children, static lung volumes were analysed and expressed as percentage of predicted value [13].

Children with normal baseline spirometry (FVC, FEV_1 and FEV_1/FVC > LLN) and positive BDR (i.e. ≥ 12% baseline FEV_1 increase) [7] were compared to children with normal baseline spirometry but negative BDR using Z-test (large sample and normal distribution). The correlation between baseline FEV_1 and post-BD FEV_1 change was studied (Pearson correlation coefficient). The ability of PF indices to distinguish positive from negative BDR cases was determined after constructing Receiver Operating Characteristic (ROC) curves.

Among a total number of 8,586 PFT performed for asthma, 7,750 (90.3%) had a documented post-BD spirometry during the study period (the remaining files corresponded to failures in the post-BD spirometry or to bronchial challenges). Baseline spirometry values were within the range of normal in 5,238 files (67.6% of files with BDR), of which 49% corresponded to a unique test per child and the others to mainly two (20%) or three (13%) PFT per child (18% with more than 3 PFT).

Characteristics of patients and results of PFT are provided in Table 1.

The frequency of inhaled corticosteroids (ICS) prescription was significantly lower in tests displaying a positive BDR compared to tests displaying a negative BDR (P<0.0001). In all the study files, baseline FEV_1 (z-score) significantly but moderately correlated to FEV_1% baseline change (r =-0.24; P<0.0001). The proportion of tests with a positive BDR was 4.9% [95% confidence interval (CI): 4.3; 5.5] among which 17.2% [95%CI: 12.6; 21.8] had a change in FVC 10% or greater versus 0.5 [95%CI: 0.4; 0.8] in tests with negative BDR (P<0.0001). When baseline Rint or sGaw were abnormal a positive BDR was observed in 15.1% [95% CI: 9.9; 20.3] and 16.8% [95% CI: 9.5; 24.1] of cases, respectively.

ROC analysis displayed similar areas under the curve (AUC) for baseline FEV_1, FEV_1/FVC, Rint and sGaw to discriminate between positive and negative BDR tests (AUC: 0.69 [95% CI 0.56; 0.83]; 0.71 [95% CI 0.58; 0.85]; 0.68 [95% CI 0.62; 0.74] and 0.71; [95% CI 0.64; 0.78], respectively; all P<0.0001).

Thresholds of 0.42 z-score for FEV_1 or -0.16 for FEV_1/FVC enabled to detect 90% of PFT with a positive BDR, and would lead to test BDR in 68.1% (positive likelihood ratio: 1.35) and 67.4% (positive likelihood ratio: 1.36) of the cases, respectively.

The vast majority of children referred for asthma to our PFT department by paediatric sub-specialists had a normal baseline spirometry, and yet they were systematically tested for BDR because predicted normal ranges have limitations. Our routine PFT practice follows international recommendations and the present results should

be transposable to other centres following these recommendations but the proportion of children with normal baseline spirometry or a positive BDR might change according to the reliability of the pre-test diagnosis.

The proportion of children with positive BDR and normal spirometry in our study was lower than that evidenced in controller naïve asthmatic children (19%) [2] or in children under ICS and in stable condition (10%) [3]. In our study we could not infer the correct use of ICS from the recorded prescription nor did we had access to asthma symptom control in the previous month, but it is most likely that ICS decreased BDR through the improvement of children's PF in these children free of acute exacerbation. One child contributed to a unique PFT in half of the files but we did not delete files from children with repeated measurements because a consistent bronchodilator response is a rare phenomenon in children with asthma (5% during a four-year follow-up [14]) and may not have introduced a major bias in the prevalence of positive BDR.

In our study, the functional pattern of children with positive BDR was consistent with the presence of a borderline central obstruction (lower FEV_1/FVC and sGaw, higher Rint) which did not exclude the possibility of a more peripheral obstruction characterised by the absence of reduction of FEV_1/FVC because of a concomitant decrease in forced expiratory volumes (lower baseline and more reversible FVC in the positive BDR tests) [10, 15]. Furthermore, in Caucasian subjects, TLC (% predicted) values were similar in both groups, while positive BDR cases had significantly higher static volumes in favour of pulmonary distension (Table 1) [15].

In conclusion, in our population, not testing bronchodilator in children with normal baseline spirometry would lead to miss a positive BDR in 4.9% of the cases, and measuring baseline resistance or sGaw could help to select children with an increased probability of positive BDR. Our results require further validation in independent populations before using the proposed thresholds (0.42 z-score for FEV_1 and -0.16 z-score for FEV_1/FVC) to skip BDR assessment in asthmatic children with normal baseline spirometry.

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Table 1- Characteristics of the 5,238 pulmonary function tests with normal baseline spirometry according to bronchodilator response

5,238 PFT in 2,343 children 1,149 children tested once 474 children tested twice 302 children tested thrice 418 tested more than thrice	**Negative BD response, n=4,983**		**Positive BD response, n=255**		**Difference between responsive and non-responsive cases**	
	Value or Mean	**SD**	**Value or Mean**	**SD**	**Mean**	**95%CI**
Sex, % boys	61.6		65.9			
Age, years	10.7	2.9	10.0	3.1	-0.7	[-1.1 ; -0.3]
ICS controller, % cases	75.3		64.3		-11.0	[-16.5 ; -5.5]
Spirometry						
Baseline						
FEV_1, L	2.19	0.74	1.92	0.75	-0.27	[-0.36 ; -0.17]
FEV_1, Z score	0.06	0.91	-0.53	0.68	-0.58	[-0.67 ; -0.50]
FVC, L	2.58	0.9	2.36	0.98	-0.22	[-0.34 ; -0.10]
FVC, Z score	0.28	0.90	-0.01	0.75	-0.28	[-0.38 ; -0.19]
FEV_1/FVC	0.85	0.05	0.82	0.05	-0.03	[-0.04 ; -0.02]
FEV_1/FVC, Z score	-0.43	0.77	-0.95	0.60	-0.52	[-0.60 ; -0.45]
After salbutamol						
FEV_1, L	2.26	0.76	2.21	0.85	-0.05	[-0.16 ; 0.05]
FEV_1, Z score	0.33	0.92	0.64	0.82	0.30	[0.20 ; 0.41]
Change in FEV_1, % baseline	3.4	3.9	15.4	4.4	12.0	[11.5 ; 12.6]
FVC, L	2.57	0.91	2.48	0.98	-0.10	[-0.22 ; 0.03]
FVC, Z score	0.25	0.91	0.46	0.84	0.21	[0.11 ; 0.32]
Change in FVC, % baseline	-0.3	3.5	5.9	6.2	6.20	[5.43 ; 6.97]
FEV_1/FVC	0.88	0.05	0.90	0.04	0.01	[0.01 ; 0.02]
FEV_1/FVC, Z score	0.10	0.76	0.26	0.68	0.16	[0.07 ; 0.24]
Interrupter resistance						
Rint, n	*1,105*		*87*			
Rint, $kPa.s.L^{-1}$	0.75	0.18	0.87	0.21	0.12	[0.08 ; 0.17]
Rint, Z score	1.01	0.88	1.56	0.86	0.55	[0.36 ; 0.74]
Rint > 1.96 Z score, % cases	13.8		31.0		17.3	[9.5 ; 25.1]
Plethysmography						
sGaw, n	*920*		*53*			
sGaw, $kPa^{-1}.s^{-1}$	1.74	0.58	1.35	0.49	-0.39	[-0.53 ; -0.26]
sGaw, Z score	-0.50	1.28	-1.38	1.09	-0.87	[-1.18 ; -0.57]
sGaw<-1.96 Z score, % cases	9.1		32.1		22.9	[16.3 ; 29.6]
Volumes (caucasian files),n	*2,125*		*79*			
TLC, L	3.85	1.11	4.01	1.19	0.18	[-0.08 ; 0.45]
TLC, % predicted	100.5	10.1	102.0	9.4	1.5	[-0.6 ; 3.6]
FRC, L	1.79	0.59	1.92	0.61	0.13	[-0.01 ; 0.26]
FRC, % predicted	95.2	15.4	99.4	15.2	4.1	[0.7 ; 7.6]
RV, L	0.89	0.30	1.00	0.33	0.11	[0.03 ; 0.18]
RV, % predicted	97.7	24.2	106.9	25.9	9.2	[3.4 ; 15.0]
RV/TLC, (%)	23.3	4.8	25.0	5.1	1.7	[0.5 ; 2.8]

BD: bronchodilator; ICS: Inhaled CorticoSteroids; FVC: Forced Vital Capacity, FEV_1: forced expiratory volume in 1 s; Rint: interrupter resistance; sGaw: specific airway conductance; TLC: Total Lung Capacity; FRC: Functional Residual Capacity; RV: Residual Volume