Effect of long-acting β-agonist on bronchodilator response in children with asthma

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"take home" message: If Long-Acting Beta 2-Agonist are not withhold before pulmonary function test in asthmatic children, its effect on baseline function will be evaluated, but significant FEV_1 reversibility will occur independently of LABA inhalation

To the editor

Spirometry is the most common pulmonary function test (PFT) used to follow asthmatic patients. It is recommended to withhold Short-Acting Beta 2-Agonists (SABA) a few hours before PFTing, and to withheld Long-Acting Beta 2-Agonists (LABA) for diagnosis purpose but not for the assessment of response to a current treatment [1]. In asthmatic children, the addition of LABA to inhaled corticosteroids (ICS) has no clear clinical benefit but it has proved to improve baseline Forced Expiratory Volume in 1 second (FEV_1)[2]. The maximal increase in FEV_1 after a single dose of formoterol was measured 3 hours after administration but the remaining effect after 12 hours would depended on the inhaled dose [3]. Finally, 25µg or 50µg of Salmeterol inhaled at 10 p.m. resulted in higher baseline pulmonary function and decrease in exercise induced bronchoconstriction 10 and 12 hours later [4]. In routine practice, children are tested with various delays since last LABA inhalation, but LABA is usually inhaled on the morning of the test (<12h before), in the evening the previous day (>12h) or on the morning the previous day or before (>24h). It is thought that children with the most recent inhalation should have the best pulmonary function and the lowest reversibility, but the latest issue has not been studied.

To study the effect of the delay since the last dose of LABA on the BDR, we prospectively and consecutively included, from May 2015 to April 2016, children 6 to 18 years of age, referred for PFT from the outpatient clinic of our tertiary paediatric hospital with typical asthma treated with an association of ICS and LABA.

Exclusion criteria were 1) SABA inhaled < 8 hours before PFT; 2) other chronic diseases potentially affecting PFT results; 3) moderate (≥ two days of rescue bronchodilator) or severe (≥ three days of oral corticosteroids) asthma exacerbation [5] within the last 7 or 15 days, respectively,

or current acute asthma symptoms; 4) patient unable to perform spirometry. Parents and patients over 8 years of age gave informed consent for the study, which was approved by the Institutional Review Board of the French learned society for respiratory medicine -Société de Pneumologie de Langue Française- (CEPRO 2015-017).

Anthropometric and clinical characteristics of asthma disease were recorded, including environmental tobacco smoke exposure (ETS), history of hospitalization for asthma flare-up, asthma exacerbations within the last three months, asthma symptom control according to the Global Initiative for Asthma (www.ginasthma.org). The child's ability to use his/her inhaler (including a demonstration using an empty disposal and questions on how he/she knew when it was empty) was determined using a standardized questionnaire. The child then performed baseline and post-BD (Salbutamol 400 µg metered-dose inhaler in a spacer) spirometry (BodyBox, Medisoft, Sorinnes, Belgium) according to international guidelines [6].

The lower normal limit (LLN) for spirometry indices was set at -1.64 z-score [7] and FEV_1 reversibility was significant if ≥ 12% predicted without absolute change criterion as children < 10 years were included [8]. Quantitative variables were compared using the Wilcoxon-Mann-Whitney test. The relationships between the delay since the last inhalation of LABA and baseline obstruction or FEV_1 reversibility were studied using Cochran–Armitage test for trend. Univariate analyses between FEV_1 reversibility and clinical characteristics, the type of inhaler used, the last dose of LABA (full dose [*ie* 12µg for Formoterol, 50µg for Salmeterol] or half dose), baseline FEV_1 and FEV_1 to Forced Vital Capacity (FVC) ratio were performed. Significant covariates at a 20% threshold were retained for the final multivariate model. The *P*-value confirmed a statistical relationship when < 0.05 (two-sided). All statistical analysis was performed with SAS software (version 9.4, SAS Institute Inc., Cary, North Carolina, USA).

We enrolled 267 patients, and secondarily excluded 7 children with unclear delay since last inhalation of LABA. 260 children (median [Q1;Q3] age 12.2 [9.6;14.9] years, 163 boys) were included in the three groups of analysis according to last LABA inhalation (<12h, n=126; 12-24 h, n=88 and > 24 h, n=46). Children were mostly Caucasian (67.7%) and African—Caribbean (19.2%). Frequencies of ETS (25.1%), history of hospitalization (39.8%), moderate or severe asthma exacerbations in the previous three months (37.8%), and use of antileukotriene medication (39.5%) were similar across groups. During the previous month, asthma was well, partly or not controlled in 84.9%, 12.0% and 3.1% of cases, respectively. A third of children were prescribed a Turbuhaler device (n=85), half had a Diskus (n=131) and a sixth a metered dose inhaler (n=44). The children demonstrated a correct use of their devices in 85.4% of cases. The last dose of LABA taken before PFT was equally full dose (52.1%) or half dose (47.9%).

The baseline and post-BD PFT results across the three groups are shown in Table 1. The logistic regression including FEV_1 reversibility as the dependent variable showed significant independent relationships with full dose of LABA inhaled (OR [95%IC]: 0.24 [0.08;0.77]; *P*=0.02), baseline FEV_1>LLN (OR [95%IC]: 0.14 [0.04;0.53]; *P*=0.003) and FEV_1/FCV>LLN (OR [95%IC]: 0.24 [0.08;0.75]; *P*=0.01). In contrast, there was no relationship between the delay since last dose of LABA and significant reversibility (12-24h OR [95%IC]: 0.54 [0.13;2.16]; *P*=0.38; >24h OR [95%IC]: 1.38 [0.41;4.64]; *P*=0.60). It is to be noted that there was no interaction between baseline FEV_1 and FEV_1/FVC (*P*=0.11), and that the molecule inhaled did not influenced the results.

The children with an inhalation technique judged as correct were younger than those with an incorrect technique (11.8 [9.3;14.3] versus 13.2 [11.8;15.4] years; *P*=0.01), but showed similar results than the whole population for all the findings.

In our study, exacerbation which is a known factor for future risk in asthma [9] was not associated to a different frequency of significant reversibility. It may be due to the relative small population studied compared to longitudinal studies showing that a low BDR during childhood is related to poor pulmonary function from childhood into adulthood [10,11]. We did not observe any relationship between FEV_1 reversibility and asthma symptom control, but there were very few children with uncontrolled asthma in our study population.

The delay since last LABA inhalation was declared, which could be a limitation, but we took great care about the schedule reported by the child and his/her parents and unreliable cases were excluded. The difference in pulmonary function in the three groups is in agreement with our assessment of the delay (Table 1).

Our results suggest that it was mainly the persistence of bronchoconstriction that influenced the occurrence of a significant reversibility independently of the delay since last LABA inhalation. The lack of reversibility under treatment might also reveal ongoing airway remodeling [12]. In contrast, the persistence of bronchoconstriction and reversibility under treatment suggests that there is still a therapeutic possibility to improve pulmonary function, especially in children taking insufficient dose of LABA.

In conclusion, baseline bronchial obstruction in children without recent exacerbation is related to a significant FEV_1 reversibility. The delay since last LABA inhalation should not interfere in the interpretation of BDR, but the dose of LABA has to be considered. However, LABA improve baseline pulmonary function and should, therefore, not be withhold before PFT if its effect on baseline function is to be evaluated.

Further studies looking at changes in clinical and PFT (including BDR) outcomes before and after the initiation of LABA treatment could give insight in persistent reversibility under treatment.

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Table 1. Baseline and post-bronchodilator FEV_1 and FEV_1/FVC, and bronchodilator response in 3 groups of children according to the delay since last LABA dose

	<12h **N=126**	**12h to 24h** **N=88**	**>24h** **N=46**	***P*-value**
Baseline FVC (z-score)	0.14 [-0.47;0.82]	0.03 [-0.69;0.79]	0.07 [-0.49;0.66]	
Baseline FEV_1 (z-score)	-0.24 [-0.89;0.46]	-0.37 [-0.92;0.58]	-0.55 [-1.38;0.10]	0.08
Baseline FEV_1/FVC (z-score)	-0.67 [-1.53;0.05]	-0.84 [-1.28;0.32]	-1.05[-1.94;-0.34]	0.05
Baseline obstruction	26 *(21)*	15 *(17)*	16 *(35)*	0.27
Post-BD FVC (z-score)	0.15 [-0.48;0.83]	-0.09 [-0.62;0.79]	0.19 [-0.44;0.67]	
Post-BD FEV_1 (z-score)	0.12 [-0.61;0.73]	0.08 [-0.57;0.91]	-0.14 [-0.53;0.55]	0.45
Post-BD FEV_1/FVC (z-score)	-0.27 [-0.84;0.72]	0.11 [-0.82;0.65]	-0.13[-1.01;0.31]	0.32
FEV_1 reversibility ≥12% Pr	10 *(8)*	4 *(5)*	7 *(15)*	0.30

Results are expressed in median [Q1;Q3]) or number *(%)*. FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 s; Post-BD: post-short acting bronchodilator inhalation; Pr: predicted value