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WILEY PEDIATRIC PULMONOLOGY

Interrupter resistance to measure dose-response to salbutamol in wheezy preschool children

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Abstract

Aim: Using a non-invasive lung function technique (interrupter resistance, Rint), we aimed to determine whether a dose-response to salbutamol could be detected in wheezy preschool children and if so, which dose of salbutamol should be administered to routinely evaluate bronchial reversibility.

Method: Wheezy children (3 to <7 years) were enrolled in a prospective multicenter study. Rint was measured at baseline, and after random assignment to a first dose (100 or 200 µg) and a second dose (cumulative dose: 400, 600, or 800 µg) of salbutamol. Data were analyzed using mixed modeling approach with an inhibitory maximal effect (I_{max}) model, to account for a sparse sampling design. Simulations were performed to predict the percentage of children with significant Rint reversibility at several doses.

Results: Final results were available in 99 children out of 106 children included. The model adequately fitted the data, showing satisfactory goodness-of-fit plots and a low residual error of 8%. Children with uncontrolled symptoms had lower I_{max} (ie, showed less reversibility) compared to children with totally/partly controlled symptoms (0.23 vs. 0.31, $P < 0.001$). Dose to reach 50% of I_{max} (D_{50}) was 51 µg. According to simulations, 88.1% of children with significant reversibility at dose 800 µg would already show significant reversibility at 400 µg.

Conclusion: Interrupter resistance was able to measure a dose-response curve to salbutamol in wheezy preschool children, which was similar to that of older patients. Young children require a high dose of salbutamol to correctly assess airway bronchodilator response, especially these with poor symptom control.

KEYWORDS
asthma & early wheeze, bronchodilation, pharmacodynamic, pulmonary function testing

1 | INTRODUCTION

Wheezing is a common clinical feature encountered in young children.[1] It may either continue throughout childhood and into adulthood, or resolve before the age of 6 years.[2] Wheezing in preschoolers is a heterogeneous condition that should not be called asthma because pathophysiology might differ from that of asthma in older children or in adults, and more importantly, because anti-asthma medications may be less effective in this age group.[3]

Short-acting beta2 agonists (SABA) are the medication most frequently used to relieve acute symptoms of asthma or to measure airway reactivity during routine pulmonary function testing (PFT).

Airway reactivity to SABA (as measured by change in Forced Expiratory Volume in 1 s (FEV_1), ie, reversibility) in a child tested for clinical symptoms suggestive of asthma, is in favor of this diagnosis.[4] However, the effect of SABA on airways is difficult to assess in preschool children with variable clinical presentation,[5] who may not correctly cooperate with spirometry, in whom criteria for reversibility are not yet well established[4,6] and the correct dose of SABA to administer is unclear.[7–14] PFT techniques which require less cooperation to assess respiratory system mechanics (the forced oscillation technique [FOT] or the interrupter technique [Rint])], are more suitable to assess preschool children[15] and previous evaluations of these techniques have reported larger bronchodilator response in asthmatics or wheezers compared to healthy children.[7–9,12,13,16] The threshold used routinely for Rint reversibility in preschool children is −35% predicted or −0.25 $kPa.L^{-1}.s$[10,16] which corresponds to a decrease larger than the within-occasion repeatability (coefficient of reproducibility from 0.17 to 0.24 $kPa.L^{-1}.s$).[9,11,17,18]

Dose-response studies have shown that bronchodilation is progressive in healthy and asthmatic adults who receive graded doses of salbutamol[19] with a maximal airway response reached for a lower dose in healthy compared to asthmatic adults.[20] Dose-response to salbutamol assessed using respiratory conductance (Grs) or FEV_1 is also able to discriminate reversibility between asthmatic subjects and subjects suffering from chronic obstructive pulmonary disease[21] because SABA do not have the same site of effect in these two conditions. Dose-response to salbutamol relationship using population pharmacodynamic (P/PD) modeling has never been studied in healthy children or in children with wheezing or asthma younger than 8 years of age, and the dose to administer in older children and in adults has been increased from 200 to 400 µg in the last spirometry guidelines.[22]

We hypothesized that if preschool wheezers exhibit a dose-response relationship to SABA as do older patients with asthma, then (1) Rint should be able to delineate the dose-response curve; (2) we could recommend the relevant dose of SABA to administer during routine PFT to assess airway reversibility in this age group. We performed a multicenter prospective study to measure bronchodilation using the Rint technique, at five different doses of salbutamol in preschool wheezers. We looked for dose-response to salbutamol using P/PD modeling with evaluation of influencing factors.

2 | METHODS

2.1 | Subjects

Children (3 to <7 years of age) recruited in PFT laboratories of the four participating hospitals had experienced at least three episodes of wheezing clearly described during the previous year. The interval from the last medication was at least 12 h for beta2 agonists, 1 week for leukotriene antagonists, and 2 weeks for oral corticosteroids. Current inhaled corticosteroid treatment was not an exclusion criterion but was included in the covariate analysis. Children were free of exacerbation and of any other chronic cardio-respiratory conditions, including bronchopulmonary dysplasia. The personal and family history was recorded and clinical examination was performed. Symptom control during the previous month was established using the four clinical items provided by the Global Initiative on Asthma (GINA − available at www.ginasthma.org) concerning day and night symptoms and reliever use. Children were then randomized into one of four dosage schedules of salbutamol (Ventoline®, Glaxo). The dosage schedules − first and second doses of salbutamol received 30 min apart − were as follows: 100 + 300, 100 + 500, 200 + 200, and 200 + 600 µg (Figure 1), delivered via a new valve-holding chamber (Vortex®, Pari, Starnberg, Germany). At baseline and 30 min after each dose, pulse oximetry (oxygen saturation [SpO_2] and heart rate) and Rint

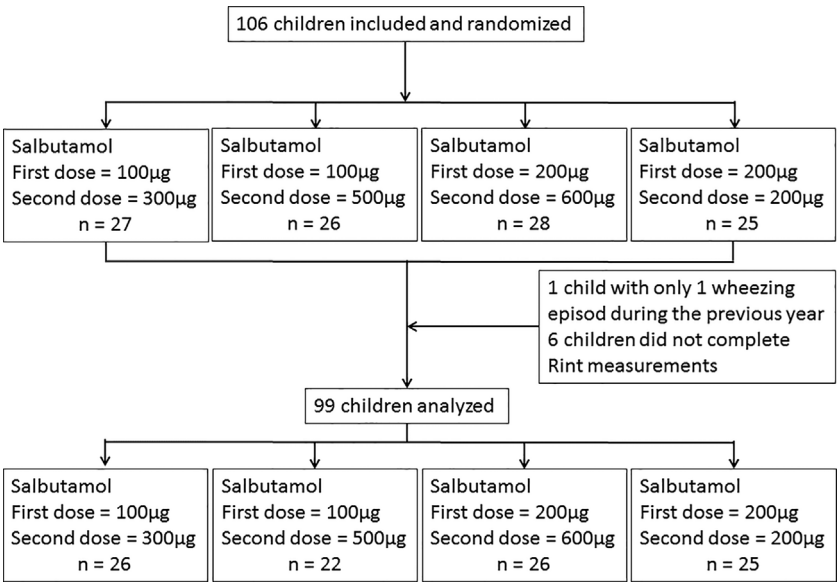

FIGURE 1 Flow of participants

measurements during expiration (MicroRint, Micro Medical Ltd, Rochester, UK, or SpiroDyn'R, Dyn'R Ltd, Aix-en-Provence, France) were recorded by an investigator blinded to the doses received by the child.

Rint acquisitions were performed and calculated as recommended.[15] The equation by Merkus et al[23] (computed from data recorded using the same two Rint devices as we used), was used to calculate z-scores from reference values.

Design evaluation used PFIM (www.pfim.biostat.fr), a software for designing longitudinal studies,[24] based on previously published data.[16,25] The estimation of the dose-response curve with adequate precision required the inclusion of 90 children with two doses per child.

The study was supported by a grant from the Programme Hospitalier de Recherche Clinique P100504, approved by the local ethics committees (CPP Ile-de-France 1, Meyer Hospital) and registered (number NCT01470755). Written informed consent was obtained from parents.

2.2 | Statistical analysis

Continuous variables were described by medians and interquartile intervals or ranges and discrete variables by numbers and percentages. Descriptive statistics were performed using SAS v9.4.

The relationship between the outcome (Rint) and salbutamol dose (D) was described using the following inhibitory sigmoid maximal effect (I_{max}) model:

$$Rint = S_0\left(1 - \frac{I_{max} \times D^{\gamma}}{D_{50}{}^{\gamma} + D^{\gamma}}\right),$$

where I_{max} is the maximal effect, D_{50} the dose to reach 50% of I_{max}, γ the sigmoidicity coefficient, and S_0 the baseline value of Rint (for D = 0).[26] Repeated Rint measurements were simultaneously analyzed in all patients by mixed effect modeling approach which can compensate for the lack of individual information by borrowing strength from the whole data, and therefore, allow for precise parameter estimation even with sparse sampling design.[27,28] Each parameter was composed of two parts: (1) a fixed effect which represented the median value of this parameter in the study population; (2) a random effect which accounted for the inter-individual variability. Model fitting and estimation of population parameters were performed using SAEM algorithm[29] in MONOLIX software v4.3.3 (www.lixoft.eu).

A covariate analysis was then performed to study the effect of the following factors: age, height, weight, sex, symptoms control, treatments with inhaled corticosteroids, leukotriene antagonists or long acting bronchodilator during last month, allergy, passive smoke during pregnancy, current exposure to tobacco smoke and history of hospitalization. Screening was performed on children without any missing values for these covariates using univariate Wald test ($P < 0.1$) followed by a forward selection based on likelihood ratio test (LRT, $P < 0.05$). To evaluate the impact of the inter-center variability, we introduced an additional random component in the model and compared this latter to the one without inter-center variability (see Online Supplementary Methods file).

Using the final model estimated on children without any missing values for the selected covariates, a simulation study determined the appropriate salbutamol dose to administer. Individual predicted Rint values were simulated (using R v3.2.2) for 5000 children at progressive doses of Salbutamol from 0 to 800 μg. We then predicted for each dose the proportions of children with different level of Rint reversibility (expressed as percentage of predicted). Details on methods and statistical analysis are available in the Online Supplementary Method file.

3 | RESULTS

Between January 2012 and June 2014, 106 children were included (52 children in Armand Trousseau Hospital, Paris, France, 33 children in Montpellier Hospital, France, 5 children in Robert Debré hospital, Paris, France, and 16 children in Anna Meyer Paediatric University-Hospital, Florence, Italy). Seven children were excluded (Figure 1) mostly because less than five correct Rint measurements were obtained at baseline or after the first administration of bronchodilator. The anthropomorphic and clinical characteristics of the remaining 99 study children are displayed in Table 1.

The allotted doses of salbutamol and the number of children randomized in each group are displayed in Figure 1. Raw values of the followed-up indices are in the Online Supplement (Supplementary Table S1). At baseline 25 children had airways obstruction (Rint z-score > 1.96), whilst after the first and second dose of salbutamol only four and one children, respectively, had persistent obstruction. A significant Rint reversibility (a decrease of at least 35% predicted) compared to baseline measurement after the first and second dose of salbutamol was present in 36 and 47 children; respectively.

Children with abnormal pulmonary auscultation on the day of the study tended to have partly controlled or uncontrolled symptoms during last month (10 [53%] and 7 [37%] children; respectively), but their Rint abnormalities and changes were similar to that of the whole population (Supplementary Table S2).

The observed Rint measurements across several doses are displayed in Figure 2 for raw values and in Supplementary Figure S1 for percent of predicted. The inter-individual variability was high and varied across doses as expected from the four-groups design structure involving different number of observations at each cumulative dose. The I_{max} model adequately fitted the data with satisfactory goodness-of-fit plots (Supplementary Figures S2–S4) and a low residual error of 8%. All population parameters reported in Supplementary Table S3 were estimated with reasonable precision but a rather important inter-individual variability for D_{50} and γ (ω above 100%).

The univariate analysis on 87 patients without any missing value for the studied covariates displayed effects of symptoms control ($P = 0.008$) and weight ($P = 0.06$) on I_{max} as well as those of height ($P = 1.3\ 10^{-7}$), age ($P = 1.7\ 10^{-5}$), weight ($P = 7.9\ 10^{-5}$) and previous hospitalization ($P = 0.004$) on S_0. By contrast, no significant effect of

TABLE 1 Characteristics of the 99 study children

	Median first and third quartiles [Q1;Q3] or (range), or number of children (%)
Age (years)[a]	4.8 (3.1;6.9)
Sex Male/female	61/38 (61.6/38.4)
Birth weight	
(g)	3398 [3020;3700]
(z-score)	0.12 [−0.50;0.88]
Weight	
(kg)	19 [17;21]
(z-score)	1.07 [−0.10;1.94]
Height	
(cm)	108.4 [104;114]
(z-score)	0.90 [0.27;1.50]
Body mass index	
($kg.m^{-2}$)	16.3 [15;17.1]
(z-score)	0.56 [−0.38;1.24]
Maternal tobacco smoke during pregnancy	8 (8.1)
Current caretakers tobacco smoke	40 (40.4)
Familial history mother/father/siblings	
Eczema (n = 98/97/77)	10/8/15 (10.2/8.2/19.5)
Asthma (n = 96/94/74)	21/23/18 (21.9/24.5/24.3)
Allergic rhinitis (n = 99/98/77)	36/27/5 (36.4/27.6/6.5)
Respiratory allergy (n = 97/91/73)	27/23/8 (27.8/25.3/11.0)
Food allergy (n = 99/95/77)	4/3/3 (4.0/3.2/3.9)
Personal history of atopy	
Eczema	42 (42.4)
Allergic rhinitis	23 (23.2)
Respiratory allergy (n = 94)	45 (47.9)
Food allergy (n = 97)	9 (9.3)
Age at first wheeze (years)	1.0 (0.1;5.8)
Episodes of wheezing before 3 years of age (n = 98)	
None	24 (24.5)
1 or 2	28 (28.6)
3 or more	46 (46.9)
Number of hospitalizations for wheezing (n = 98)	
None	76 (77.6)
1 or 2	11 (11.2)
3 or more	11 (11.2)
Triggers for recurrence of wheezing (n = 98)	
Airways infection	89 (90.8)
Exercise	39 (39.8)
Clinical efficacy of SABA to relieve acute symptoms according to parents (n = 98)	82 (83.7)
Inhaled corticosteroids during last month	62 (62.6)
Long acting bronchodilator during last month	35 (35.3)
Number of days with long acting bronchodilator	30 [15;30]
Anti-leukotriens during last month	10 (10.1)
Oral corticosteroids during last month	4 (4.0)
SABA during last month	30 (30.3)
Number of days with SABA	5 [2;10]
Symptoms control during last month (n = 92)	
Controlled	37 (40.2)
Partly controlled	35 (38.1)
Uncontrolled	20 (21.7)
Abnormal pulmonary auscultation	19 (19.3)

SABA, short-acting beta2 agonists.
[a]Results are from the total population or n specified when missing data.

the inhaled corticosteroid treatment regime was found on any of the parameters; I_{max} (P = 0.13), D_{50} (P = 0.80), S_0 (P = 0.87). Following a forward selection based on LRT, effects of symptoms control (P = 0.03) and weight (P = 0.01) on I_{max} and height ($P < 10^{-5}$) on S_0 were found: uncontrolled symptoms and low weight decreased I_{max} whereas height negatively influenced S_0. There was no clinical relevance of weight and

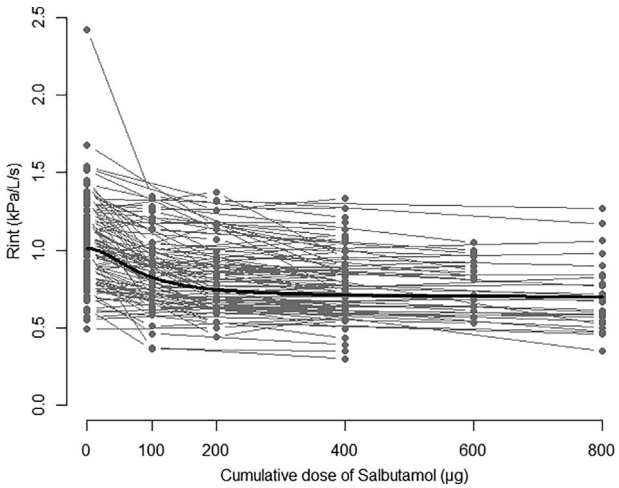

FIGURE 2 Spaghetti plot of observed Rint values versus salbutamol doses in 99 children included in the analysis. The gray dots correspond to the observed Rint measurements. The black curve is the mean dose-response curve predicted by the basic model without covariate

height variations as 5 kg or 10 cm deviations (which are unlikely short-term variations) from median weight and height would result in less than 20% increase or decrease in I_{max} and S_0. The population parameter estimates of the final model are reported in Supplementary Table S3 for 92 patients without any missing value for the selected covariates (final [RSE%] values I_{max} 0.23 [11]; D_{50} 51 [30] µg). In this final model, the maximal effect I_{max} was increased by 35% in children with totally/partly controlled symptoms as compared to those with uncontrolled symptoms (median 0.31 vs. 0.23, $P < 10^{-7}$) (Supplementary Table S4). As a consequence, the maximal Rint decrease expected for an infinite salbutamol dose (expressed in % of Rint predicted) was significantly different between these two groups (median 41% vs. 31%, $P < 0.001$) (Figure 3). It is to be noted that I_{max} was not significantly correlated to S_0 (% predicted) ($r = -0.03$, $P = 0.7$).

The results of the model accounting for the inter-center variability showed that our selected covariates remained similarly significant without modification of the goodness-of-fit (Supplementary Table S5 and Online Supplementary Results file).

Using the final population model (assuming only one level of variability across individuals), 5000 individual dose-response profiles were simulated to predict the changes in Rint after multiple doses of salbutamol, including low doses that were not tested during the study (Supplementary Table S6, Figures 4 and S5). Among children with significant Rint reversibility (at least 35% predicted decrease) at dose 800 µg according to the simulation, 74.8%, 82.8%, 88.1%, and 94.7% would already show significant reversibility at dose 200, 300, 400, and 600 µg respectively. The convention in reversibility testing is the use of a dose able to cause a maximal effect in at least 80–85% of patients. (see Online Supplementary Results file for more details).

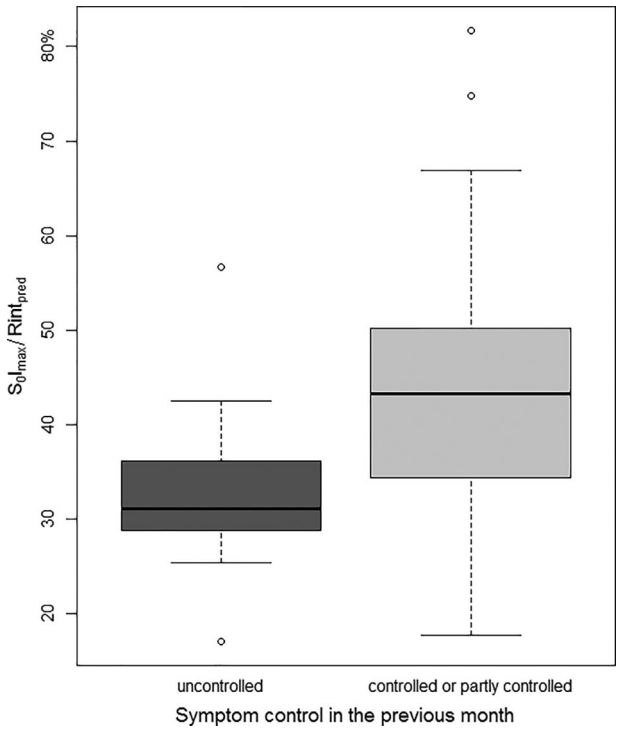

FIGURE 3 Distribution of individual maximal effects expressed through the maximal decrease of Rint from baseline, according to symptoms control during the previous month in 92 children without any missing value for the significant covariates selected in the final model. From the individual S_0 and I_{max} values estimated from the final model with covariates, the individual maximal decreases of Rint (at an infinite dose) from baseline, were calculated as (S_0*I_{max}) over the predicted Rint value for a given height

4 | DISCUSSION

The present multicenter study in preschool children confirms that: (1) Rint can measure dose-response to salbutamol in preschool wheezers; and (2) the clinically relevant dose of salbutamol to be administered for routine PFT is at least 400 µg. These results suggest that preschool wheezers share similarities with older asthmatic patients. Another new finding of this study is the influence of symptom control on dose-response to SABA with less responsiveness in not controlled children.

Preschool children with recurrent wheezing exhibit different courses in phenotypes, lung function,[30] and therapeutic requirements[3,31] which requires the development of tools to objectively assess disease characteristics.[32] We studied children with a range of wheezing patterns (Table 1), but we checked for potential influencing factors of severity such as previous hospitalization, allergy, and tobacco exposure and did not find evidence for any role of these covariates.

Despite the lack of studies on the clinical efficacy of SABA in preschool children,[5] SABA is the only medication recommended to be used for acute symptoms[3] and there is clinical evidence that during

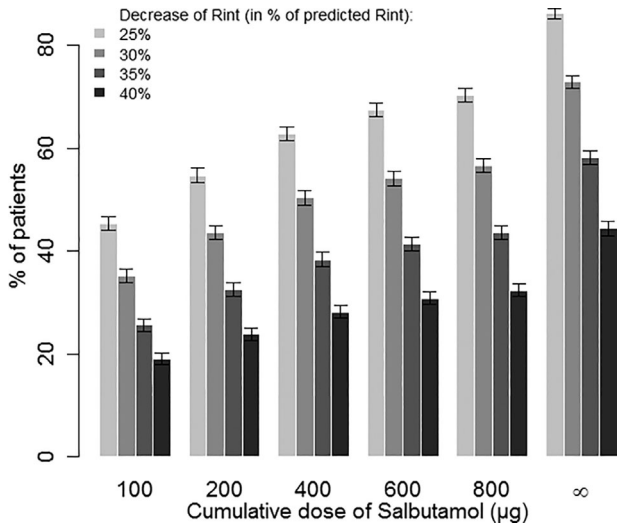

FIGURE 4 Rint decrease at several doses of Salbutamol in 5000 patients simulated using the final model. Proportion of children (from 5000 patients simulated using the final model) with a decrease in Rint (% predicted Rint for a given height) of at least 25%, 30%, 35%, and 40% respectively at several doses of Salbutamol, as well as the 95% confidence intervals of these proportions

respiratory exacerbation dose-response to salbutamol exists. However, in this situation, it is not possible to distinguish between a pure pharmacological dose-response, and progressive bronchodilation which allows a gradual increase in SABA bronchial deposition and increasing effect with time (and doses). We included children free of exacerbation which does not preclude loss of symptom control ($n = 20$) or baseline airway obstruction ($n = 25$), however a higher proportion showed significant Rint reversibility after first dose ($n = 36$) and second dose ($n = 47$) of salbutamol. This is in agreement with previous observations that reversibility of respiratory resistance is more sensitive than baseline measurements[8,9,12,13,16,33] and does not relate the detection of a dose-response at high dose of SABA to the enrolment of mainly obstructed subjects.

Patients with asthma exhibit a dose-response curve which requires a higher dose of bronchodilator to reach maximum effect than that required in healthy subjects[19,20] and respond with a maximal effect larger than that of subjects with obstructive pulmonary diseases other than asthma.[21] We found a dose to reach 50% of I_{max} (D_{50}) of 84.0 μg (RSE 24%) (Supplementary Table S3), a value similar to the mean D_{50} calculated in asthmatic adults (82.8 μg, RSE 34%) and significantly higher than D_{50} in healthy subjects (22.8 μg, RSE 6%; $P < 0.01$).[23] After adjustment for significant influencing factors, we still found a D_{50} higher (51 μg, RSE 30%) than that of healthy adults. In a population of asthmatic subjects (8 to 65 years) recruited with low baseline FEV_1,[34] a fixed coefficient of sigmoidicity of 2 (similar to ours: 1.96) was found to best fit the dose-response data with high variability of other parameters (D_{50}, Imax) as in our study, indicating that the Rint technique was not responsible for the variability recorded but revealed a true inter-subject dose-response variability. The distribution of the groups randomization was not different across centers, but we also looked for inter-center difference in the model. We showed that the covariates selected in our final model remained statistically significant in an alternative model accounting for inter-center variability, (see Online Supplementary Results file).

In our study, we modeled the raw Rint observed values to avoid biased assessments of the actual response as recommended for P/PD modeling.[35] However, as our analysis was adjusted on the patient's characteristics determining the reference equations for Rint (sex and height), our main findings still hold when using Rint percentages of predicted instead of raw values (see Online Supplementary Results file).

In the absence of P/PD modeling in control children in the present study or in literature, the maximal effect measured ($I_{max} = 0.23$) can only be compared to Rint reversibility detected in healthy preschool children after different dosages of bronchodilator (median 0.07 after 400 μg salbutamol,[8] mean 0.16 after 500 μg terbutaline[7] and 0.11 after 200 μg salbutamol[16]). From this comparison, it is probable that preschool wheezers have both a larger maximal reversibility than their healthy counterparts, and require a higher dose to reach this maximal. Therefore, using too low a dose of SABA during PFT could hamper the ability of Rint to correctly diagnose children with a significant reversibility.

Among the different clinical characteristics, only symptoms control in the last month had an impact on the maximal effect of SABA. Whether it is the poor effect of bronchodilator that explained the poor control or vice versa cannot be inferred from our data. Among possible explanations, early remodeling should be considered and explored by the follow-up of these children.[36] Another cause for lower I_{max} could be the effect of regular use of SABA or long-acting bronchodilator as an effect of genetic polymorphisms in beta2-receptor (Arg/Gly16).[37] Thirty five children had daily bronchodilator treatment, and to explore this issue the present study is currently being replicated with an additional genetic analysis of Arg/Gly16 polymorphism in beta2-receptor (Eudract number 2014-001978-33).

4.1 | Strength and limits of the study

Our study has some limitations. First, our study was not designed to describe the ability of dose-response to salbutamol to distinguish healthy from sick children and we did not include healthy children. We know from earlier studies conducted in adults that healthy subjects have a dose-response to low dose of salbutamol[19,20] and a lower maximal effect of SABA compare to asthmatics.[20] We previously published data on Rint reversibility in healthy preschool children measured after 200 μg of salbutamol[10,25] (a higher dose than that achieving maximal airways response in healthy adults, that is, 110 μg[20]). At this moderate dose, Rint reversibility was already significantly smaller in healthy children compared to asthmatic children (−11.2 ± 15.2% and −8.0 ± 14.6% in healthy vs. −18.6 ± 13.6% in wheezy children). It is therefore probable that I_{max} is smaller in healthy young children compared to young wheezers.

In order to correctly assess the dose-response of each dose using Rint we carried out post-bronchodilator measurements 30 min after the inhalation (see Online Supplementary Methods file) which may be slightly later than routine clinical testing practices. The possible additional bronchodilator effect occurring between 15 and 20 min and 30 min should be small, and could be compensated for by giving a higher than 400 μg dose.

In mild to moderate asthmatic school children there is evidence that inhaled corticosteroids decrease the bronchodilator response via the improvement of baseline FEV_1.[38] No such data exist for younger wheezers. Although nearly two-thirds of the study children had received inhaled corticosteroids in the previous month, a dose-response to salbutamol was detected. Whether I_{max} and D_{50} would have been higher if only children without asthma controller had been included cannot be extrapolated from our data, but inhaled corticosteroids were not found to significantly influence the dose-response relationship. On the other hand, including children with and without current inhaled corticosteroids treatment, we were able to define the minimal dose of bronchodilator to administer for a bronchodilation test for both populations of children.

This is the first study aiming to establish the dose-response relationship to salbutamol in wheezy preschool children using interrupter resistance. Children in this age group are challenging to test because they do not tolerate prolonged PFT measurements, making rich data difficult to obtain. Therefore, we first proposed an informative sparse design using model-based optimal design theory. According to the EMA guideline for pharmacokinetics in the pediatric

population,[39] the mixed effect modeling approach used with optimal sparse sampling may replace conventionally designed studies with rich sampling. However, this approach requires well-designed studies with adequate data collection to obtain informative samples. The appropriateness of our model was evaluated using several well-established goodness-of-fit tools.[40] Second, we did not plan additional children in order to validate the model we were looking for and, therefore, we could not split the study dataset into a training set and a testing set with sufficiently large sample-size for both data subsets. A further validation study is in progress (Eudract number 2014-001978-33) but so far, even in adult subjects, this type of study is lacking.

In conclusion, using the Rint technique we found that preschool wheezers had a similar pattern of bronchodilator response to older asthmatic subjects. Because of the properties of the dose-response curve, the dose of salbutamol to administer to perform a bronchodilation test should be not less than 400 µg and may be more in preschool children with poor symptom control. Our results, obtained using modeling and simulation, highlighted the usefulness of these model-based techniques in dose-response studies with rare but informative data and sparse designs. They also encourage further studies in children to confirm our findings, and to facilitate personalized management of wheezy preschool children.

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CONFLICTS OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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