



HAL
open science

Relationship between baseline and post-bronchodilator interrupter resistance and specific airway resistance in preschool children

Pauline Mauger-Hamel, Cécile Du Boisbaudry, Karelle Léon, Zarrin Alavi, Marie-Agnès Giroux-Metges

► To cite this version:

Pauline Mauger-Hamel, Cécile Du Boisbaudry, Karelle Léon, Zarrin Alavi, Marie-Agnès Giroux-Metges. Relationship between baseline and post-bronchodilator interrupter resistance and specific airway resistance in preschool children. *Annals of Allergy, Asthma and Immunology*, 2020, 124, pp.366 - 372. 10.1016/j.anai.2020.01.003 . hal-03489922

HAL Id: hal-03489922

<https://hal.science/hal-03489922>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

**Relationship between Baseline and Post-bronchodilator Interrupter
Resistance and Specific Airway Resistance in preschool children.**

Pauline Mauger-Hamel, MD^{a-b}, Cécile Du Boisbaudry, MD^b, Karelle Léon, PhD^c, Zarrin Alavi MSc, MEng^d, Marie-Agnès Giroux-Metges MD, PhD^{b-c}

^a Service de Pédiatrie Générale, CHRU de Brest, 2 avenue Foch, F29200 Brest France

^b Service des Explorations Fonctionnelles Respiratoires, CHRU de Brest, 2 avenue Foch, F29200 Brest France

^c UFR médecine et sciences de la santé, ORPHY EA 4324, Univ Brest, F29200 Brest - France

^d CIC 1412, CHRU de Brest, Boulevard Tanguy Prigent, F29200 Brest France

3) Corresponding Author Information:

Pauline Mauger-Hamel

Service de pédiatrie, CHRU BREST hôpital Morvan 2 avenue Foch, 29200 BREST

E-mail : pauline.mauger1@gmail.com

phone number : +33(0)2 98 22 33 89

fax number : + 33(0)2 98 22 30 39

4) Conflict of interest : none

5) Funding source : none

6) Clinical trial registration : NCT02563210 (ClinicalTrials.gov identifier).
<https://clinicaltrials.gov/ct2/results?cond=&term=NCT02563210&cntry=&state=&city=&dist=>

7) Keywords: airway resistance; preschool child; pulmonary function test (PFT); bronchodilator response

8) Abbreviations/acronyms :

AUC : Area Under the Curve

BDR : Bronchodilator Response

CI : Confidence Interval

FEV1 : forced expiratory volume in one second

GINA : Global Initiative for Asthma

PFT : pulmonary function test

Rint : interrupter resistance

ROC : Receiver Operating Characteristics curves

sRaw : specific airway resistance

9) Word count : 3090

10) Figures : 5

11) Tables : 3

1 INTRODUCTION

2 Measurement of lung function is an essential component of the management of school
3 children (> 6 years old, yo) and adults with chronic lung diseases such as asthma or cystic
4 fibrosis.¹ Nevertheless, this measurement is hard to achieve in preschool children (< 6 yo).
5 Indeed, it would be difficult to have active cooperation of a preschool child whose muscular
6 capacity and motor coordination are not fully developed to yield an optimal forced exhaling
7 and inhaling outcome.

8 To address this issue, different techniques requiring only mild active co-operation from the
9 children have been developed and evaluated among children under 6 yo.¹

10 Interrupter resistance (Rint) is nowadays a popular lung function technique routinely used to
11 measure respiratory resistance in young children. Rint is a non invasive procedure during
12 which alveolar pressure and flow is estimated through the mouth. The former is measured
13 during a brief and sudden airflow interruption. The latter is measured during tidal breathing
14 just before the interruption. The calculated Rint includes components of lung tissue and chest
15 wall resistance as well as respiratory tissue viscoelasticity.^{2,3}

16 Plethysmographic specific airway resistance (sRaw) is a useful method for detection of lung
17 disease in young children.⁴ sRaw can be measured during tidal breathing from the
18 relationship between simultaneous measurements of airflow and change of plethysmographic
19 pressure without any special breathing maneuvers against an airway occlusion.⁵

20 Both Rint and sRaw techniques are safe, feasible and reproducible.^{4,6-9} Rint and sRaw values
21 show a strong correlation with clinical status and FEV1 results in children 3 to 13 yo.^{6,10-13}

22 The Bronchodilator Response (BDR) routinely assessed during Pulmonary Function Test
23 (PFT) can provide an objective and sensitive criterion for the diagnosis of asthma.¹⁴

24 Reference equations for calculation of Rint and sRaw as well as the definition for airway
25 resistance expressed as z-scores were published in 2010 by the asthma UK initiative.^{15,16}

26 Several studies have reported cut-off values for the change in Rint, interpreted as positive
27 BDR^{6,17} and only one reported a cut-off for the change in sRaw as positive BDR.¹²

28 Thus, we aimed to study the relationship between Rint and sRaw baseline measurements, and
29 the agreement between Rint and sRaw in diagnosis of bronchial obstruction and BDR in
30 accordance with the latest guidelines in children aged 3 to 6 years.¹⁵ Our second objective
31 was to determine our cut-off for the change in sRaw as positive BDR in our population.

32

33 **METHODS**

34 **Subjects**

35 One hundred thirty children 3 to 6 yo referred to our Pediatric Pulmonary Function Test unit
36 for assessment of airway function (PET) were consecutively and prospectively included from
37 October 15, 2015 to May 22, 2017. Children < 90 cm of height were excluded in accordance
38 with gold standard height for Rint and sRaw. Patients and their parents received
39 comprehensive information about the objectives of the study, their rights to refuse to
40 participate in the study or the possibility of withdrawal at any time. Patient information and
41 non-opposition form was obtained from the legal representative or parent. The ethics
42 committee approved the study on August 25, 2015 (reference number RB 15.181). This work
43 was declared to the French commission for information technology and civil liberties (CNIL).
44 Trial Registration: NCT02563210 (ClinicalTrials.gov identifier).

45

46 **Procedures**

47 During consultation, an interview with each child and parents was conducted by the
48 physician. The children were then weighed, measured (height) and examined by the physician
49 before carrying out resistance measurements. For patients with asthma, baseline clinical
50 status was as follows: asymptomatic for well-controlled asthma or symptomatic for poorly or

51 partially controlled one according to clinical GINA Criteria 2015. Each child was randomized
52 for order of Rint and sRaw measurements. A BDR test was performed for each child who did
53 not take bronchodilator within 12 hours of testing. Measurements were performed 15 min
54 after administration of the bronchodilator (400 µg of Salbutamol administered using a
55 metered dose inhaler and a spacer device Aerochamber +®, GlaskoSmithKline).

56

57 **Rint measurements**

58 Rint was measured using a SpiroDynR apparatus (SpiroDyn'R® 3.2.0.5 version, LtD,
59 Toulouse, France) calibrated daily for flow. In accordance with the guideline by the
60 American Thoracic Society/European Respiratory Society, Rint was measured during a 100
61 ms occlusion that occurred during expiration, using linear-back extrapolation of mouth
62 pressure to estimate alveolar pressure.¹⁸

63 During measurements, the child was seated and asked to breathe quietly, connected to the
64 flowmeter by a mouthpiece and a bacteriological filter (total dead space of 40 ml) with a nose
65 clip. Measurements were performed with the head held in a neutral position, cheeks and chin
66 held by a third party hands (parent or physician).

67 After 3 breathing cycles at the same volume and frequency, the flow interruption was
68 triggered by the operator and the flow and buccal depression measurements were performed.
69 Validation of the measurements was done in accordance with international guidelines.⁶ In
70 line with the literature, ten measurements of Rint were required to reach seven validated ones
71 thus a mean Rint with an intrasubject coefficient of variation $\leq 20\%$.

72

73 Rint absolute values were expressed in $\text{kPa}\cdot\text{L}^{-1}\cdot\text{s}$ and z-score according to the latest
74 international guidelines.¹⁵ Baseline bronchial obstruction was defined as z-score > 2 . BDR
75 was positive if the change in Rint was $\geq 0.26 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{s}$ from the absolute value (Δ_{abs}) or \geq

76 1.25 z-score (Δz -score) or $\geq 32\%$ from the baseline measurement ($\Delta\%bas$), $\geq 35\%$ from the
77 predicted value ($\Delta\%pre$).^{10,16}

78

79 **sRaw measurements**

80 sRaw were measured using MasterScreen (Jaeger® standard model, a constant-pressure body
81 plethysmograph) daily calibrated and during tidal breathing and without manual adjustment
82 of tangents.^{16,19} In the closed cabin, the child was in sitting position, the head in neutral
83 position, the cheeks held with the hands. The child was coached to reach a respiratory rate of
84 30 to 45 breaths/min, connected to the pneumotachograph by a mouthpiece and a
85 bacteriological filter (total dead space of 40 ml) with a nose clip. In line with the literature, a
86 mean of 20 breathing cycles with an intra-subject coefficient of variation $\leq 20\%$ and a stable
87 ventilatory level were required.^{6,20} sRaw was calculated from the relationship between
88 simultaneous flow measurements at the airway opening and the alveolar pressure
89 modification reflected by the pressure inside the plethysmograph.¹⁹ sRtot was computed
90 between two points of maximum plethysmographic pressure during respiratory cycle.¹⁶ The
91 validated measurement was the median of the 3 measurement medians (i.e. medians of three
92 series of at least 5 correct curves). Compensation for body temperature and barometric
93 pressure at water vapor saturation (BTPS conditions) was achieved electronically. The airway
94 measurement method was done during tidal breathing in line with that described by Kirkby et
95 al (2010) and no manual adjustment of tangents was applied.

96 sRaw absolute values were expressed in $kPa \cdot s^{-1}$ and z-scores in accordance with the latest
97 international recommendations.¹⁶ Baseline bronchial obstruction was defined as z-score > 2 .
98 In line with the reported reference methodology by Nielsen et al¹² and Raywood et al²¹ the
99 cut-off for sRaw positive BDR was set at 32%, from the baseline measurement ($\Delta\%bas$).

100

101 **Statistical Analysis**

102 Categorical variables were expressed as frequency and percentage. Continuous variables
103 were expressed as means and standard deviations (SD) or as median and quartiles depending
104 on the data distribution.

105 Changes in Rint and sRaw values were assessed using the paired Student t test. Correlation
106 tests were performed by using the Pearson correlation coefficient. Symptomatic and
107 asymptomatic asthmatic patient groups were compared using the Student t test.

108 We assessed the agreement between Rint and sRaw by calculating the Cohen's Kappa
109 coefficient and its 95% confidence interval (CI).

110 To determine our cut-offs of sRaw positive BDR, we used Receiver Operating Characteristics
111 (ROC) curves. ROC curves were generated to determine the highest concomitant sensitivity
112 and specificity of sRaw cut-off with decrease in sRaw expressed in four different ways: 1) the
113 absolute value (Δ_{abs}), 2) the baseline measurement ($\Delta_{\%bas}$), 3) the predicted value ($\Delta_{\%pre}$)
114 and 4) the z-score ($\Delta_{z-score}$).

115 In the absence of healthy children (without any respiratory symptoms), we arbitrarily chose
116 to use Rint as the reference measurement for airway resistance evaluation in our preschool
117 children population. This was done for optimal prediction of BDR with maximal Youden
118 Index. The Area Under the Curve (AUC) was measured to assess how well sRaw could
119 distinguish between two diagnostic groups (positive BDR or negative BDR). Sensitivity,
120 specificity, negative, and positive predictive values were calculated and presented with 95%
121 CI.

122 P-values < 0.05 were considered statistically significant. Statistical analyses were carried out
123 using SAS Version 9.4.

124

125

126 RESULTS

127 Participants

128 One hundred thirty patients were included in this study. All were European Caucasian
129 children. The mean age of children was 4.9 years (SD = 0.63) with 9.2% between 3 and 4
130 years. Fifty eight per cent of children were male. Among these patients, 28 (21.5%) were
131 referred for asthma suspicion with symptoms of atypical asthma, 63 (48.5%) for the
132 management of a viral induced asthma, 38 (29.2%) for the management of allergic asthma
133 and 1 (0.8%) for bronchopulmonary dysplasia. Among the one hundred one patients referred
134 for management of asthma (viral induced or allergic), 57 were symptomatic with poorly or
135 partially controlled asthma and 44 were asymptomatic with well-controlled asthma. Most
136 children (73.8%) already had treatment(s) (bronchodilators, inhaled corticosteroids or
137 montelukast) before the measurements. Figure 1 displays the flow of children throughout the
138 study.

139

140 Baseline measurements

141 Baseline measurements of Rint and sRaw were obtained for 120 (92.3%) children. The
142 excluded children (7.7%) were those who refused to blow into the flowmeter, or enter the
143 cabin or were not able to maintain a respiratory rate between 30 and 45 per min for sRaw.

144 Baseline Rint and sRaw z-scores were significantly different (mean \pm SD: -0.4 ± 2.47 and $-$
145 0.6 ± 0.96 , respectively; $P < 0.01$) (Table 1).

146

147 Correlation between baseline Rint and baseline sRaw z-scores was significant according to
148 Pearson correlation coefficient $r = 0.5$ ($P < 0.01$). Baseline bronchial obstruction defined as
149 abnormally high Rint (z-score > 2) was present in 18 patients although baseline obstruction
150 defined as abnormally high sRaw (z-score > 2) was present in 1 patient. Only this one patient

151 had bronchial obstruction detected by both Rint and sRaw (Figure.2). The agreement between
152 the two techniques was poor, Cohen Kappa coefficient at 0.09 [95% CI:-0.08: 0.26].

153

154 In children with diagnosis of asthma (viral induced and allergic), Rint z-scores of
155 symptomatic group were higher than those of asymptomatic patients: 0.2 ± 2.34 vs. $-1.1 \pm$
156 2.74 respectively, $P = 0.012$. Similarly, sRaw z-scores in the symptomatic group were
157 significantly higher than in the asymptomatic group: -0.2 ± 0.93 vs. -0.9 ± 0.96 respectively,
158 $P = 0.002$ (Figure 3).

159

160 **Bronchodilator response**

161 In 101 children who performed both techniques after bronchodilator administration, Rint and
162 sRaw (absolute value and z-score) significantly decreased from the baseline ($P < 0.01$; Table
163 1).

164 The changes after administration of bronchodilator expressed with different methods are
165 shown in Table 1.

166 Rint positive BDR was present in 29 patients whereas sRaw positive BDR was present in 17
167 patients. Eleven patients had positive BDR with both techniques (Figure 4). The agreement
168 between Rint and sRaw in positive BDR was fair (Cohen's Kappa coefficient: 0.33; 95% CI:
169 0.13; 0.54).

170

171 Among 101 asthmatic children who performed baseline measurements, 83 performed BDR
172 test with Rint and sRaw. The others had taken bronchodilator treatment 12 hours before or
173 were unable to carry out Rint or sRaw measurement after taking bronchodilator. There were
174 significant differences in Rint and sRaw between symptomatic and asymptomatic children
175 when changes from the baseline were expressed in absolute value and in z-score, ($P < 0.01$).

176 There was no difference between the two groups when results were expressed as percentage
177 of predicted value ($P > 0.05$; Table 2).

178

179 Our cut-off for sRaw to predict a positive BDR was determined as follows: a decrease \geq
180 28%, according to change from the baseline; a decrease $\geq 35\%$, according to change from the
181 predicted value; a decrease $\geq 0.27 \text{ kPa}\cdot\text{s}^{-1}$, according to change from the absolute value; a
182 decrease ≥ 1.07 when expressed in z-score.

183 The sensitivity, specificity, positive predictive value and negative predictive value for each
184 cut-off point are shown in Table 3.

185 The most optimal diagnostic performance (sensitivity, specificity, positive and negative
186 predictive values) of sRaw change in predicting positive BDR was either a decrease from the
187 absolute sRaw of $\geq 0.27 \text{ kPa}\cdot\text{s}^{-1}$ or a decrease from the baseline sRaw of $\geq 28\%$. The
188 sensitivity, specificity and AUC obtained for the cut-off from the baseline sRaw of $\geq 28\%$
189 was respectively 60%, 86% and 0.718 (Figure 5). AUC figures for other cut-off values were
190 not shown.

191 The cut-off of $\geq 28\%$ decrease in sRaw showed a mean sensitivity of 60% (Table 3) detecting a
192 decrease of 32% in Rint from baseline.

193

194 **DISCUSSION**

195 This is the only work that aimed at evaluating the agreement between Rint and sRaw
196 measurements in diagnosis of bronchial obstruction and positive BDR in a very young (mean
197 age: 4.5 yo) population of children with all respiratory indications including symptomatic and
198 asymptomatic asthma. Despite their different physiological meaning,^{2,3,11} breathing cycle
199 measurement expression in z-scores could be evaluated for correlation and agreement of
200 diagnosis.

201 We observed a poor agreement for bronchial obstruction and fair agreement for BDR. Several
202 previous studies have reported large inter- and intra-individual variability for baseline
203 Rint.^{3,13,20} For sRaw this inter-individual variability was 10 % in pre-school children.²² In
204 our study we could observe that the standard deviation in Rint measurement was higher than
205 the sRaw standard deviation. This could be explained by the fact that Rint z-score takes into
206 account the height (i.e. quite variable in 3-6 yo children) compared with sRaw z-score which
207 takes into account the age. Nevertheless we found a strong linear correlation between the two
208 measurement methods expressed by Pearson coefficient ($r = 0.5$). To the best of our
209 knowledge, the study by Nielsen et al. has been the only work comparing Rint and sRaw.¹²
210 They showed a strong correlation between Rint and sRaw in height and clinical status.¹²
211 Other studies have reported a correlation between Rint or sRaw measurements and clinical
212 status (healthy or asthmatic) or spirometry data (i.e. the gold standard in lung function test in
213 older children).^{6,10,12,17,23}

214
215 As we were interested in comparing the two types of measurements in routine conditions, we
216 included all-comer children regardless of the reason for consultation at our Pulmonary
217 Function Test Unit. This could have biased our selection due to the absence of healthy
218 children. The measurements of Rint and sRaw seemed to be consistent with those of the
219 literature even though our population was different.^{4,6,20,24,25} Consistent with other works, our
220 subgroup of symptomatic asthmatic children had baseline values of Rint and sRaw higher
221 than those of asymptomatic children.^{6,12} With regard to sRaw measurement, Coutier et al
222 showed that sRaw measured during tidal breathing is overestimated compared with that
223 during panting in children. In our study, measurement during tidal breathing was chosen for
224 its feasibility with ease among our younger population (3-6 yo) compared to that of Coutier et
225 al. (6.5-11.5 yo).²⁶

226 The agreement between Rint and sRaw was fair (Cohen Kappa coefficient = 0.33) in positive
227 BDR but higher than that in baseline z-scores.

228 This was consistent with other works reporting that BDR is better than resistance baseline z-
229 scores to highlight bronchial hyper reactivity and hence leading to better prevention,
230 diagnosis and management of asthma in children.^{1,21}

231

232 Given our clinical practice, we believe that clinical status in 3-6 yo population can be
233 regarded as a reliable criterion when screening for positive BDR. Our population was only
234 composed of children consulting for a symptomatic respiratory problem. Given our study
235 design and methodology, we did not include healthy children. Our goal was to distinguish
236 BDR negative children from BDR positive children. Rint measurement, with threshold points
237 defined according to clinical status, is the most used technique for airway resistance
238 evaluation in preschool children. To that end, we chose Rint cut-off as the reference
239 measurement to estimate the cut-off points for change in sRaw.

240

241 In our study we found that the most optimal diagnostic performance (sensitivity, specificity,
242 positive and negative predictive values) of sRaw change in predicting positive BDR was a
243 decrease $\geq 28\%$ from the baseline. In the study by Nielsen et al, the cut-off for the change in
244 sRaw for detection of positive BDR was expressed, as a decrease of: 32 % from the baseline
245 and 25% from the predicted value.¹²

246 Our cut-off ($\geq 28\%$ decrease from the baseline) was close to that proposed by Nielsen et al.¹²

247 Therefore, in future studies with similar population (children with symptomatic respiratory
248 problems) our suggested cut-off could be used to detect BDR and improve therapeutic
249 decision-making.

250 This estimation of change in sRaw (percentage from the baseline) seems to be the most
251 reliable with regard to sensitivity, specificity, negative and positive predicted values for
252 determining the BDR diagnosis. The least reliable estimation seems to be the change of sRaw
253 according to percentage of predicted value. Indeed, changes in Rint and sRaw expressed in
254 percentages of predicted values are used to predict FEV₁ reversibility in schoolchildren able
255 to perform spirometry and not to predict the clinical status of children < 6 yo.^{10,23} This study
256 has some limitations. The prevalence of bronchial obstruction was low in our pediatric
257 population because of the characteristics of our inclusive population. This could have limited
258 the statistical power of our study. No controlled healthy children were available, to compare
259 Rint and sRaw between patient cases and controls. This would have put forward the interest
260 of these measurements in detection of children with uncertain diagnosis of asthma or with
261 atypical symptoms of asthma.

262

263 Our measurement method to obtain sRaw was in line with that described in the literature.^{16,19}
264 However, there seems to be a lack of consensus on its reliability of use in young children. We
265 believe that multicenter, prospective, longitudinal studies should be conducted to reach a
266 consensual measurement method for sRaw and to assess the reliability of such method.²⁷

267

268 BDR measurement of sRaw in our study was defined as the change in Rint and not that of
269 BDR positivity in clinical status. Consequently, our results (i.e. no cut-off value for BDR)
270 cannot be extrapolated to the general population.

271

272 The poor agreement between the Rint and sRaw measurements further highlights that a single
273 airway resistance measurement method cannot confer optimal diagnosis of bronchial
274 obstruction. Indeed, additional airway measurement methods such as bronchodilation test

275 should be performed. Further larger sample, prospective studies are required to confirm our
276 cut-off point in sRaw change (decrease ≥ 28 % from the baseline measurement) for positive
277 BDR and to assess its clinical relevance. Then, it would be interesting to assess the usefulness
278 of airway resistance measurements in therapeutic decision for asthma management.

REFERENCES

1. Rosenfeld M, Allen J, Arets BH et al. American Thoracic Society Assembly on Pediatrics Working Group on Infant and Preschool Lung Function Testing. An official American Thoracic Society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. *Ann Am Thorac Soc*. 2013;10(2):S1-S11.
2. Oswald-Mammosser M, Charloux A, Donato L et al. Interrupter technique versus plethysmography for measurement of respiratory resistance in children with asthma or cystic fibrosis *J Pediatr Pulmonol*. 2000;29(3):213-220.
3. Merkus PJ, Mijnsbergen JY, Hop WC, de Jongste JC. Interrupter resistance in preschool children: measurement characteristics and reference values. *Am J Respir Crit Care Med*. 2001;163(6):1350-1355.
4. Bisgaard H, Nielsen KG. Plethysmographic measurements of specific airway resistance in young children. *Chest*. 2005;128(1):355-362.
5. Dab I, Alexander F. A simplified approach to the measurement of specific airway resistance. *Pediatr Res*. 1976;10(12):998-999.
6. Beydon N, Amsallem F, Bellet M et al. French Pediatric Programme Hospitalier de Recherche Clinique Group. Pre/postbronchodilator interrupter resistance values in healthy young children. *Am J Respir Crit Care Med*. 2002;165(10):1388-1394.
7. Bridge PD, Ranganathan S, McKenzie SA. Measurement of airway resistance using the interrupter technique in preschool children in the ambulatory setting. *Eur Respir J*. 1999;13(4):792-796.
8. Lombardi E, Sly PD, Concutelli G et al. Reference values of interrupter respiratory resistance in healthy preschool white children. *Thorax*. 2001;56(9):691-695.
9. McKenzie SA, Chan E, Dundas I et al. Airway resistance measured by the interrupter technique: normative data for 2-10 year olds of three ethnicities. *Arch Dis Child*. 2002;87(3):248-251.
10. Beydon N, Mahut B, Maingot L et al. Baseline and post-bronchodilator interrupter resistance and spirometry in asthmatic children. *Pediatr Pulmonol*. 2012;47(10):987-993.
11. Nielsen KG. Plethysmographic specific airway resistance. *Paediatr Respir Rev*. 2006;7 (suppl 1):S17-19.
12. Nielsen KG, Bisgaard H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. *Am J Respir Crit Care Med*. 2001;164(4):554-559.

13. Black J, Baxter-Jones AD, Gordon J, Findlay AL, Helms PJ. Assessment of airway function in young children with asthma: comparison of spirometry, interrupter technique, and tidal flow by inductance plethysmography. *Pediatr Pulmonol.* 2004;37(6):548-553.
14. McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. *Eur Respir J.* 2000;15(5):833-838.
15. Merkus PJ, Stocks J, Beydon N et al. Reference ranges for interrupter resistance technique: the Asthma UK Initiative. *Eur Respir J.* 2010;36(1):157-163.
16. Kirkby J, Stanojevic S, Welsh L et al. Asthma UK. Reference equations for specific airway resistance in children: the Asthma UK initiative. *Eur Respir J.* 2010;36(3):622-629.
17. Mele L, Sly PD, Calogero C et al. Assessment and validation of bronchodilation using the interrupter technique in preschool children. *Pediatr Pulmonol.* 2010;45(7):633-638.
18. Beydon N, Davis SD, Lombardi E et al. American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med.* 2007;175(12):1304-1345.
19. Jerzyńska J, Janas A, Galica K, Stelmach W, Woicka-Kolejwa K, Stelmach I. Total specific airway resistance vs spirometry in asthma evaluation in children in a large real-life population. *Ann Allergy Asthma Immunol.* 2015;115(4):272-276.
20. Beydon N, Pin I, Matran R et al. French Paediatric Programme Hospitalier de Recherche Clinique Group. Pulmonary function tests in preschool children with asthma. *Am J Respir Crit Care Med.* 2003;168(6):640-644.
21. Raywood E, Lum S, Aurora P, Pike K. The bronchodilator response in preschool children: A systematic review. *Pediatr Pulmonol.* 2016;51(11):1242-1250.
22. Brussee JE, Smit HA, Koopman LP et al. Interrupter resistance and wheezing phenotypes at 4 years of age. *Am J Respir Crit Care Med.* 2004;169(2):209-213.
23. Mahut B, Peiffer C, Bokov P, Delclaux C, Beydon N. Use of specific airway resistance to assess bronchodilator response in children. *Respirology.* 2011;16(4):666-671.
24. Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A. NAC Manchester Asthma and Allergy Study Group. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med.* 2005;171(3):231-237.
25. Belgrave DC, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A. Trajectories of lung function during childhood. *Am J Respir Crit Care Med.* 2014;189(9):1101-1109.
26. Coutier L, Ioan I, Sadegh-Eghbali A et al. Flow dependence of specific airway resistance and diagnostic of asthma in children. *Pediatr Pulmonol.* 2015;50(11):1107-1112.

27. Robinson PD, Stocks J, Marchal F et al. Poor standardisation of plethysmographic specific airways resistance measurement despite widespread use. *Eur Respir J.* 2015;46(6):1811-1814.

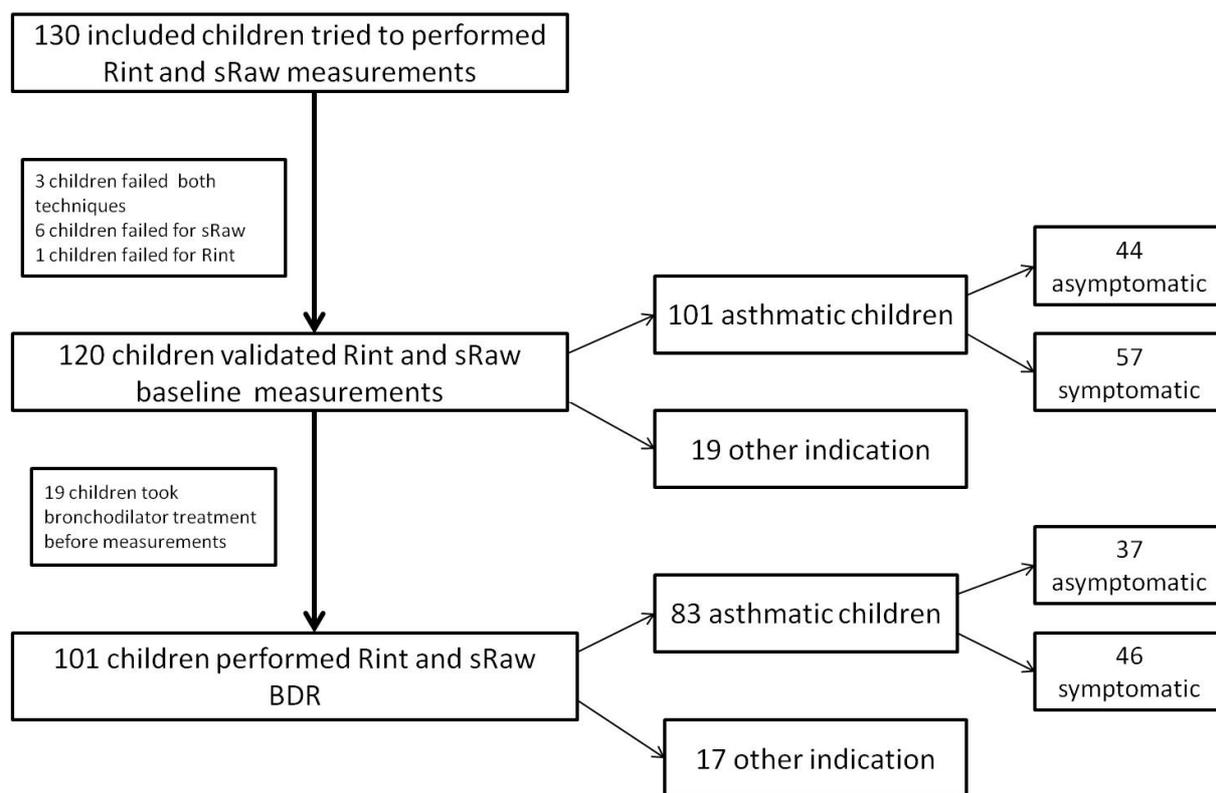


Figure 1.

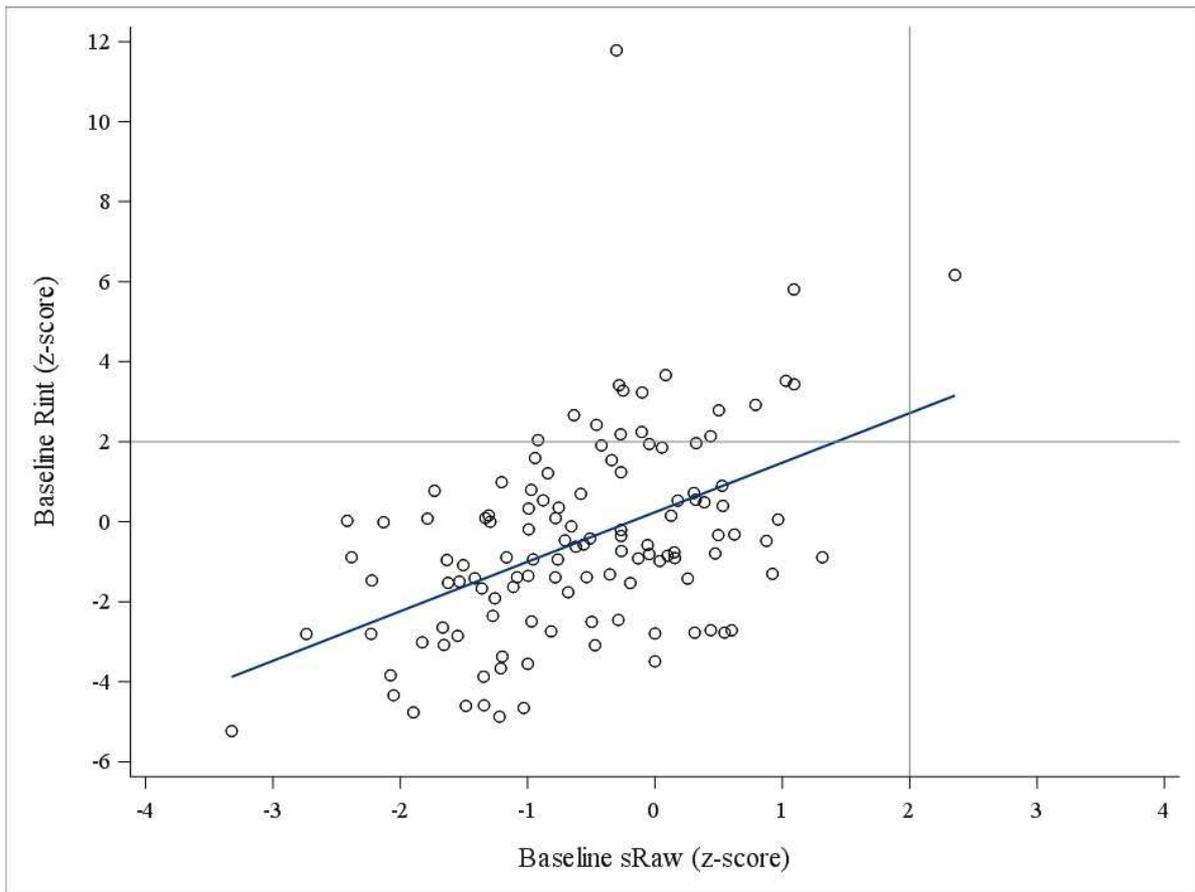


Figure 2.

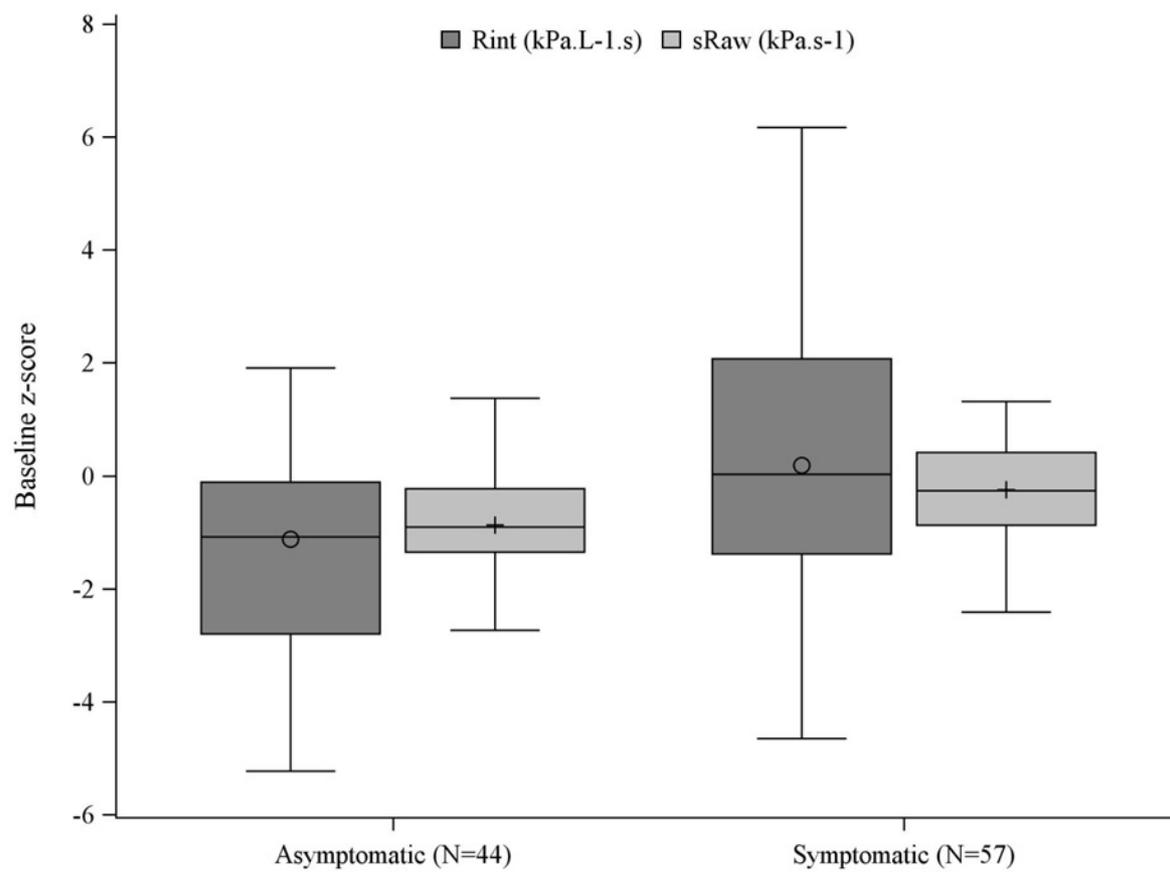


Figure 3.

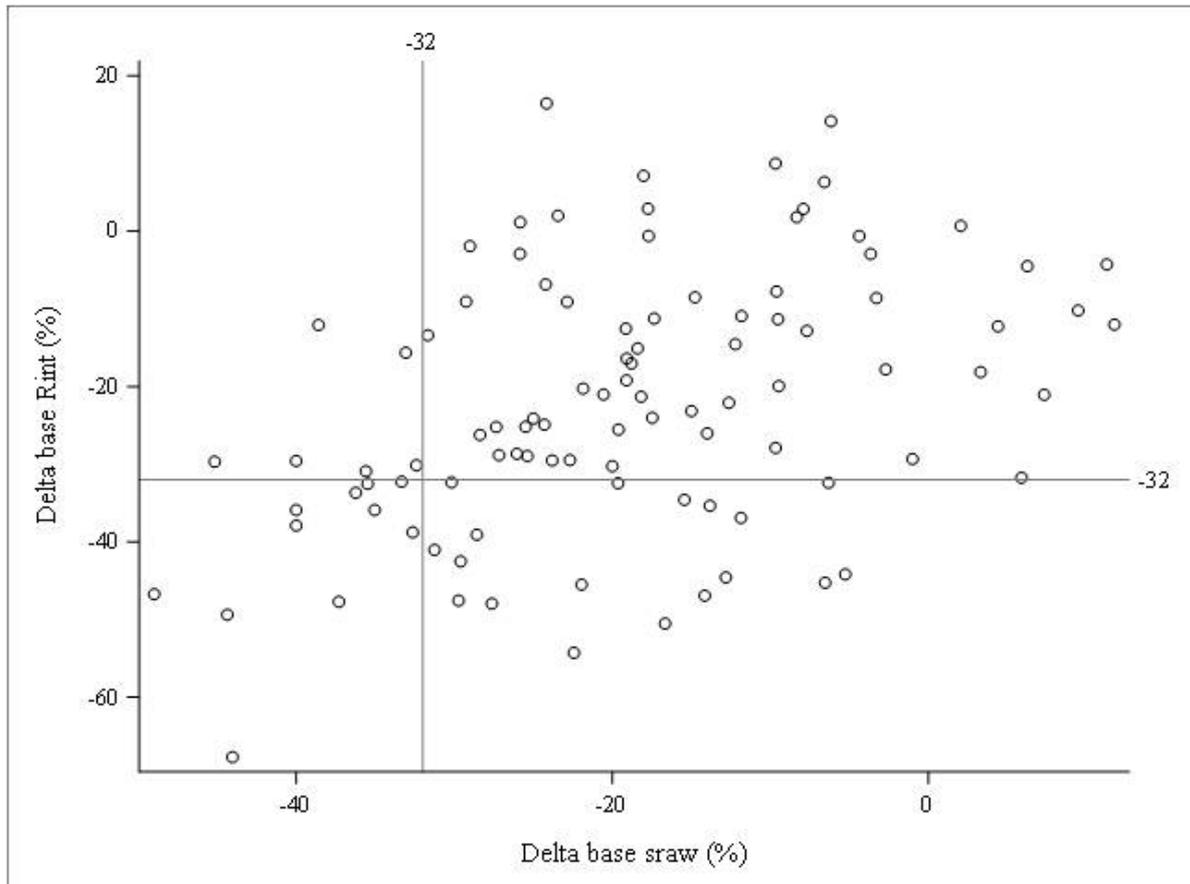


Figure 4.

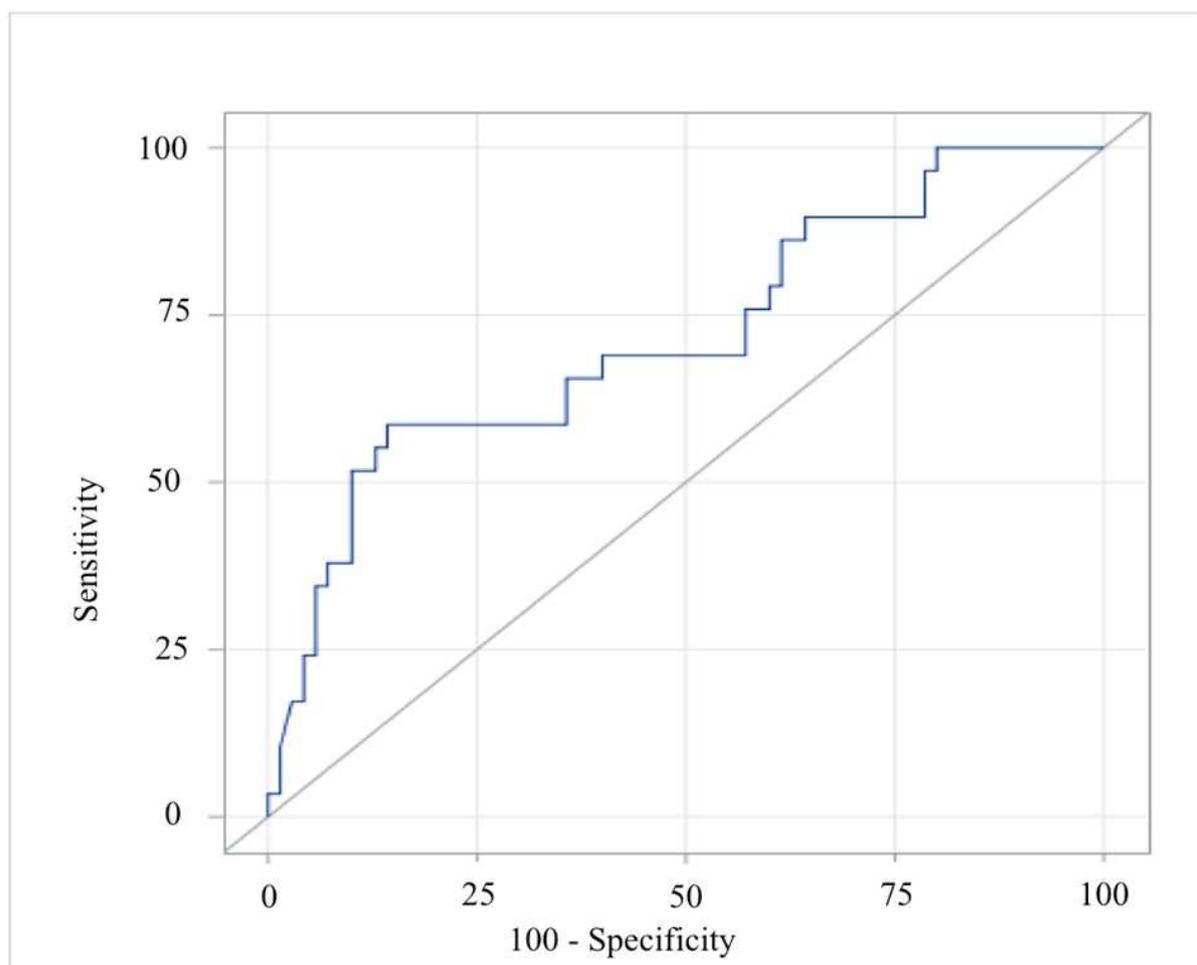


Figure 5.

Table 1

Measurements of Interrupter Resistance and Specific Airway Resistance at Baseline and after administration of bronchodilator.

	Baseline (n = 120)		Post bronchodilator (n = 101)		Changes after administration of bronchodilator (n = 101)			
	abs value	z-score	abs value	z-score	Δ abs value	Δ z-score	Δ % bas	Δ % pre
Rint (kPa.L ⁻¹ .s)	0.9 ± 0.22	-0.4 ± 2.47*	0.7 ± 0.17*	-2.8 ± 1.96*	-0.2 ± 0.17	-2.3 ± 1.96	-21.6 ± 16.56	-15.1 ± 20.34
sRaw (kPa.s ⁻¹)	1.1 ± 0.22	-0.6 ± 0.96*	0.9 ± 0.14*	-1.3 ± 0.83*	-0.2 ± 0.19	-0.7 ± 0.90	-19.0 ± 13.39	-27.9 ± 11.29

Results are expressed as mean ± standard deviation.

Rint, interrupter resistance; sRaw, specific airway resistance. Abs value, absolute value; Δ abs, change from absolute value; Δ % bas, change expressed as percentage from baseline measurement; Δ % pre, change expressed as percentage of predicted value; Δ z-score, change in z-score.

Table 2

Changes after administration of bronchodilator in 83 asthmatic children who performed post bronchodilator Rint and sRaw measurements.

	Asymptomatic (n = 37)	Symptomatic (n = 46)	<i>P</i> -value
Δ Abs Rint (kPa.L ⁻¹ .s)	-0.1 ± 0.15	-0.3 ± 0.17	<0.01
sRaw (kPa.s ⁻¹)	-0.2 ± 0.14	-0.3 ± 0.20	<0.01
Δ % bas Rint	-15.6 ± 16.91	-27.7 ± 15.52	<0.01
sRaw	-14.2 ± 11.17	-23.1 ± 12.74	<0.01
Δ % pre Rint	-16.9 ± 20.14	-14.5 ± 21.39	0.61
sRaw	-16.5 ± 11.26	-17.2 ± 13.10	0.80
Δ z-score Rint	-1.5 ± 1.71	-3.1 ± 2.03	<0.01
sRaw	-0.3 ± 0.71	-1.0 ± 0.93	<0.01

Results are expressed as mean ± standard deviation.

Δ abs, change from absolute value; Δ % bas, change expressed as percentage from baseline measurement

Δ % pre, change expressed as percentage of predicted value; Δ z-score, change in z-score.

Table 3

Sensitivity, Specificity, Negative and Positive Predictive Values (%) and their (95%CI) and area under the curve for Bronchodilator response calculated using sRaw considering Rint cut-offs as the reference measurement.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
Δ abs (≥ 0.27 kPa.s ⁻¹)	60 [43; 76]	77 [65; 86]	62 [45; 77]	76 [64; 85]	0.748
Δ % bas (≥ 28 %)	60 [40; 75]	86 [75; 92]	63 [43; 80]	83 [73; 91]	0.718
Δ % pre (≥ 35 %)	44 [20; 70]	76 [65; 85]	26 [11; 47]	88 [78; 94]	0.547
Δ z-score (≥ -1.07)	83 [66; 94]	45 [33; 58]	45 [33; 58]	83 [66; 94]	0.694

Δ abs, change from absolute value; Δ % bas, change expressed as percentage from baseline measurement; Δ % pre, change expressed as percentage of predicted value; Δ z-score, change in z-score; PPV, positive predicted value; NPV, negative predictive value; AUC, area under the curve