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Interrupter resistance short-term repeatability and bronchodilator response in preschool children

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Summary
Interrupter resistance (Rint) technique can be easily and successfully performed in preschool children. The establishment of Rint short-term repeatability is essential to interpret any Rint change after a pharmacological intervention.
Aims of the study: In preschool children with asthma or chronic cough: (1) to assess two indices of short-term repeatability: (a) intra-measurement and (b) within-occasion between-test repeatability; (2) to study the relationship between short-term repeatability and bronchodilator response (BDR).
Results: Rint intra-measurement repeatability assessed by the coefficient of variation was similar at baseline and after bronchodilator in asthmatics and in coughers (median 10% and 12%, respectively). There was no significant difference between asthmatics and coughers for both coefficient of repeatability (CR) (0.25 kPa L^{-1} s and 32% of predicted vs 0.16 kPa L^{-1} s and 21% of predicted, respectively) and BDR (median −14.7% vs −21.1% of predicted, respectively). However, in 20% of the study children, baseline variability of Rint modified the significance of the BDR.
Conclusion: In the present study, Rint short-term repeatability was similar to that of previous studies. Similar Rint repeatability in coughers and in asthmatic children favored the use of asthmatic CR for both populations, and a −35% cut-off as a positive BDR. In 20% of study children, baseline Rint variability could influence the significance of the BDR. In order to improve assessment of BDR using Rint, further studies are needed (1) to compare the variability of Rint to other resistance measurement techniques and (2) to define the best method for Rint calculation and for expression of BDR.

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Introduction

Interrupter resistance (Rint) is an easy technique to assess resistance of the respiratory system. It can be used in preschool children unable to perform reliable spirometry but old enough to accept quiet breathing through a mouthpiece. Reference values have been established in preschool children, and exhibit a large inter-individual variability.[1–3] However, in preschool children with recent history of wheezing or medical diagnosis of asthma, Rint has been shown to be significantly higher than in healthy children.[3–6] Rint value is considered as abnormal when it is outside the 95% CI of the normal distribution, i.e., *Z*-score higher than 2. In stable condition, only few sick children have abnormal values.[4,7,8] Many asthmatic children, especially those taking anti-asthma medication, exhibit normal baseline Rint value, but have an exaggerated bronchodilator response (BDR) as compared to that of healthy subjects.[4,7] However, the overlap between Rint changes in asthmatic and normal children after bronchodilator administration precludes a straightforward interpretation of the BDR.

The ability of Rint to detect more readily abnormal BDR than baseline bronchoconstriction relies on the knowledge of the short-term repeatability (or variability) of the technique in sick children, and on the establishment of BDR in healthy ones. Rint short-term repeatability reflects the variability of the measuring instrument and the biological variability of the disease. Only a Rint change greater than the short-term repeatability can be attributed to a pharmacological intervention and not to the variability of the method or of the disease. The short-term repeatability is assessed by the calculation of the intra-measurement variability, and the within-occasion between-test repeatability with a time interval similar to that used between baseline and post-bronchodilator measurements. Rint intra-measurement coefficient of variation has been found to be 10–16%, with small or no influence of health status or bronchodilator (BD) administration.[2–4,9,10] Results of within-occasion between-test repeatability yielded variable results depending on the study population and on the design of the study.[1,7,11,12] Finally, BD effect should be compared to that of placebo effect. This issue has been studied in a few studies that showed no Rint change after placebo administration in children with cough or asthma, as well as in healthy children.[5,11,13]

The main aim of the present study was to establish Rint short-term repeatability in asthmatic children and in children with chronic cough in order to determine the significance of Rint changes and the clinical relevance of Rint variability on BDR assessment. We hypothesized that short-term variability might be different in asthmatic children as compared to that of coughers, because asthmatic children may have a larger spontaneous variability in airway caliber and because they may use anti-asthma medications.

Methods and subjects

Subjects

We prospectively recorded preschool children (2–6-year-old) referred for BDR, between May 2005 and May 2006. They were either stable asthmatic children or children with chronic cough.

The diagnosis of asthma was based on typical asthma symptoms such as recurrent wheeze and breathlessness resolving spontaneously or with an inhaled bronchodilator. Chronic cough was defined as non-productive cough, without evidence of any other relevant disease, for at least 6 weeks or for more than five episodes per year. The only exclusion criterion was the presence of an acute exacerbation during the last 4 weeks for asthmatic children. Physical examination, including height and weight measurements, was performed on the day of the study and all children were free from wheezing. Doses and timing of medication were recorded for all children, and asthmatic children that had received short-acting or long-acting bronchodilator during the previous 8 and 24 h, respectively, were excluded.

Methods

Rint measurement was performed as previously described (SpiroTeq, Dyn'R, Toulouse, France).[2] Briefly, mouth pressure was recorded during a 100 ms occlusion that occurred during expiration, and Rint was calculated using the linear back extrapolation method. Rint value was the mean of at least seven correct measurements with respect to child position, movement and to the aspect of the pressure curve. Two sets of baseline measurements (RintB1 and RintB2) were performed 10 min apart without any intervention between the two measurements. Post-bronchodilator measurement (RintBD) was performed 10 min after BD administration (400 μg of salbutamol administered using a metered-dose inhaler and a spacer; Volumatic, Glaxo, Badoldesloe, Germany).

Statistical analysis

Intra-measurement variability was assessed by the calculation of the coefficient of variation (CV); $CV = SD/mean \times 100$. The within-occasion between-test variability was assessed from the variability of two sets of measurements without any intervention. The coefficient of repeatability (CR) was 2SD of the differences between the two sets of measurements performed in the same group of children. Rint *Z*-scores [(measured value−fitted mean)/fitted SD)] were calculated using previously published reference data.[2]

Rint changes and CRs were expressed as absolute values, percentage of predicted, and *Z*-scores. Data were expressed as frequencies (percentages) for categorical variables and as median, interquartile range (IQR) and range for continuous variables. Comparisons of continuous variables between groups were made using the paired or unpaired Wilcoxon test as appropriate. Spearman's correlation test was used to describe the overall correlations between Rint *Z*-scores and CV. The relationship between age and CV was studied by linear regression. The difference in Rint and CRs between the two groups was assessed by ANOVA. To determine the effect of age on the variance, the absolute residuals of all data were regressed on age. All tests were two-tailed and *P*-values less than 0.05 were considered statistically significant. Analyses were computed using SAS 9.1 software package (SAS Institute, Cary, NY, USA).

Results

Subjects

Fifty-one asthmatic preschool children, and 32 preschool children with chronic cough, all referred for BDR assessment, were studied. There was no difference in anthropomorphic data between the children of the two groups (Table 1). Twenty-four (47%) asthmatic children regularly inhaled corticosteroids, one (2%) asthmatic had a long-acting bronchodilator treatment, and six (12%) used short-acting bronchodilator on a regular basis. At the time of the test, short-acting and long-acting bronchodilators were withdrawn for 8 and 24 h, respectively. None of the children with chronic cough received any anti-asthma medication.

Intra-measurement variability

The CVs of Rint measurements at baseline and after BD in asthmatics and in coughers are shown in Table 2. There was no significant difference in baseline CVs between groups, and CVs did not change from baseline after BD administration in each group. In the two groups, bronchial obstruction, assessed by Rint *Z*-score, was not related to the corresponding Rint CV. There was no relationship between the age of the study children and the Rint CV.

Table 1 Anthropomorphic data in preschool children with asthma and with chronic cough.

	Asthmatic ($n = 51$)	Coughers ($n = 32$)
Girls/boys	17/34	17/15
Age (years)	5.1 [4.2; 5.8] (3.4; 6.7)	5.1 [4.3; 5.7] (3.4; 6.8)
Height (cm)	110 [103.3; 115] (95; 123)	109 [106.5; 116] (97; 122)
Weight (kg)	20 [16.5; 21] (13; 27)	20 [17.5; 21.5] (15; 26)

Results: median [interquartile range—IQR] (range).

Between-test variability

RintB1 for all the study children are shown in Table 3. Baseline RintB1 value was higher in asthmatic children than in children with chronic cough, but the difference between the two groups did not reach significance ($P = 0.11$). Children with significant increased RintB1 (i.e. *Z*-score > 2) were six asthmatics, and one cougher. The median [IQR] time intervals between RintB1 and RintB2 measurements were 10 [8; 30] min and 13 [10; 20] in asthmatic children and in coughers, respectively. In the two groups, there was no significant difference between RintB1 and RintB2. The difference between RintB1 and RintB2 was not related to the level of Rint value (Figure 1(a and b)). The difference between RintB1 and RintB2 was not related to the baseline bronchial obstruction assessed by RintB1 or by mean RintB1RintB2, both expressed as *Z*-scores (data not shown). The highest CR was found in asthmatic children (Table 3). However, the difference between asthmatics and coughers' CRs did not reach statistical significance ($F = 2.08$; $P = 0.15$). In the two groups, CR was unrelated to age ($P = 0.85$).

Post-bronchodilator changes

Rint decrease after BD in 79 children is shown in Table 4. There was no difference between post-BD Rint change in asthmatic children and in children with chronic cough. In asthmatic children, current inhaled corticosteroids treatment did not modify the magnitude of the BDR (−17 [−39.1;

Table 2 Rint coefficients of variation at baseline and after bronchodilation.

	CV B1 (%)	CV B2 (%)	CV BD (%)
Asthmatic ($n = 51$)	10 [8; 13] (5; 16)	11 [9; 13] (5; 19)	12 [9; 13] (4; 17)
Coughers ($n = 32$)	11 [9; 14] (4; 18)	11 [9; 14] (6; 21)	12 [10; 14] (7; 23)

Results: median [IQR] (range).CV B1: intra-measurement coefficient of variation of the first baseline Rint measurement; CV B2: intra-measurement coefficient of variation of the second baseline Rint measurement; measurements B1 and B2 performed 10 min apart. CV BD: post-bronchodilator Rint intra-measurement coefficient of variation.

Table 3 Baseline Rint measurements and between two sets of measurements (median [IQR] (range)), and coefficient of repeatability (CR = 2SD of differences).

	RintB1 (kPa L^{-1} s)	RintB1 (% predicted)	RintB1 (*Z*-score)	RintB1–B2 (kPa L^{-1} s)	CR (kPa L^{-1} s), (% predicted), (*Z*-score)
Asthmatic ($n = 51$)	0.91 [0.81; 1.08] (0.65; 1.31)	119.2 [102.2; 134.6] (91.8; 162.1)	0.9 [0.1; 1.4] (−0.4; 2.5)	−0.01 [−0.07; −0.09] (−0.49; 0.22)	0.25, 32.1, 1.4
Coughers ($n = 32$)	0.86 [0.83; 0.94]* (0.69; 1.26)	113.7 [105.3; 121]* (85.3; 155.8)	0.6 [0.2; 0.9]* (−0.7; 2.5)	0.01 [−0.05; 0.09] (−0.16; 0.17)	0.16, 22.1, 0.9

CR: coefficient of repeatability = 2SD of the differences between two baseline measurements. RintB1 higher in asthmatic children than in coughers; $P = 0.03$.

−11.4]% vs −13.6 [−26.5; −5.7]% with and without corticosteroids, respectively). Four asthmatic children and the cougher with baseline Rint *Z*-score > 2 had a significant BDR (i.e. greater than the CR). Asthmatics' CR (32% of predicted) was close to the previously published −35% of predicted cut-off that best distinguished healthy from asthmatic children.[4] However, in 16 (20%) of the study children, the significance of the BDR varied according to whether RintB1 or RintB2 was considered as baseline value (Figure 2).

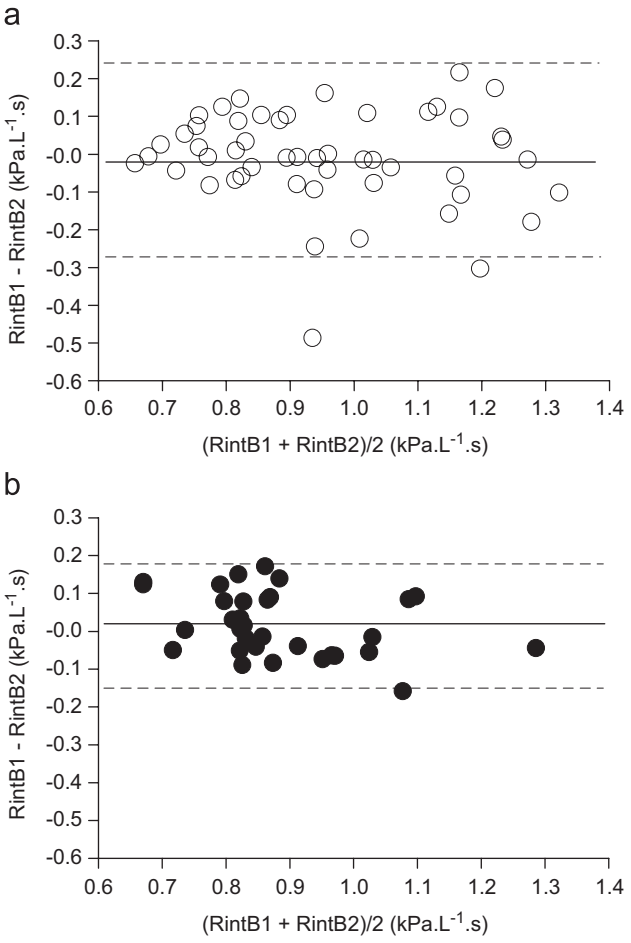

Figure 1 Bland–Altman plots of individual differences between paired baseline measurement (RintB1 and RintB2) against mean values of RintB1 and RintB2 in asthmatic children (open circles, Figure 1a) and in children with chronic cough (closed circles, Figure 1b). The solid lines indicate the mean difference between paired measurements and the dashed lines indicate 95% limits of agreement (i.e. the coefficient of repeatability).

Discussion

We established the short-term repeatability of the Rint technique in preschool children. The main findings of the present study were: (1) Rint intra-measurement variability in preschool children was not related to age, health status or airway caliber; (2) the within-occasion between-test repeatability was not related to health status or to current inhaled corticosteroids treatment; (3) Rint variability was in line with previous published data; (4) coefficients of repeatability were not different between coughers and asthmatics; and (5) the magnitude of the Rint variability may overlap the bronchodilator response in stable asthmatics and in coughers.

Subjects

Asthmatic children

In the present study, and in line with other studies,[4–6] a majority of asthmatic children (88.2%) had a baseline Rint within the range of predicted values. Moreover, the Rint value was unrelated to the anti-asthma medication use. The large distribution of Rint in healthy subjects[1–3] and the more peripheral bronchial obstruction in mild asthmatic children[14] may explain this finding, and is in favor of possible

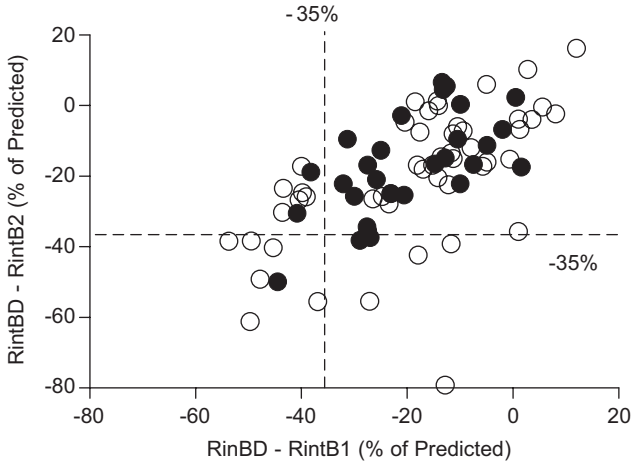

Figure 2 Bronchodilator response calculated using RintB1 or using RinB2 in asthmatics (open circles) and coughers (closed circles). Dotted lines are the previous published cut-off (−35% of predicted).[4] Values in the lower left and upper right panel represent similar Rint decreased significance whatever the baseline value (RintB1 or RintB2) used. Values in the upper left or lower right panel represent discrepancies between the two calculation methods.

Table 4 Post-bronchodilator change in Rint.

	Rint BD–B1 (kPa L^{-1} s)	Rint BD–B1 (% predicted)	Rint BD–B1 (*Z*-score)
Asthmatic ($n = 50$)	−0.13 [−0.22; −0.07] (−0.44; 0.11)	−14.7 [−27.1; −7.9] (−53.7; 12.0)	−0.7 [−1.2; −0.4] (−2.5; 0.6)
Coughers ($n = 29$)	−0.17 [−0.22; −0.08] (−0.36; 0.01)	−21.1 [−27.6; −10.5] (−44.5; 1.6)	−0.9 [−1.2; −0.44] (−2.0; 0.1)

Results: median [IQR] (range).Rint BD-B1: difference between Rint post-bronchodilator (BD) and Rint baseline (B1) values expressed in three different ways.

normal Rint value in asthmatic children with mild bronchoconstriction.

Chronic coughers

We included children with respiratory symptoms but without asthma, because Rint variability might be different due to the spontaneous variability of bronchial tone in asthmatic children as compared to that of non-asthmatic children. Chan et al.[7] did not found any correlation between health status and short-term repeatability in 18 healthy children, 28 coughers and 39 wheezers, aged 2–10 years. In the present study, intra-measurement and between-measurements repeatability did not differ significantly between coughers and asthmatic children, although the Rint CR was slightly higher in asthmatics. Only few studies have compared BDR between asthmatic children and coughers. In line with our results (Figure 2), Chan et al. found that more asthmatic children than coughers had a significant BDR (larger than the Rint CR).[7] However, as opposed to our results, Chan et al. found a significantly larger BDR in asthmatics than in coughers (22.6% vs 17.1% of predicted) (Table 4). This discrepancy could be ascribed to the anti-asthma medication used in the present study, where none of the asthmatics were under long-term treatment in Chan et al.'s study.

Intra-measurement variability

Rint CVs at baseline and after bronchodilator were within the range of previously published values.[2–4,9,10,15,16] We confirmed that age, health status or airway caliber did not affect the magnitude of CVs.[2,4,9] In our study, the CV tested the consistency of the couple "child-technician" to perform the Rint measurement. Although, different technicians participated to the present study; each child performed the Rint measurements with the same technician throughout the test. In previous studies, Rint values and Rint repeatability were not modified with respect to the assessment by different investigators.[3,11,12,17] In our laboratory, the Rint measurements are performed by trained technicians according to a written procedure that has not changed in the past years.[2]

Between-test repeatability

The calculated CR in asthmatic children was similar to previously published CR in preschool wheezers and coughers (0.25 vs 0.24 $kPa\,L^{-1}\,s$),[1,16] but slightly lower than CR in healthy preschool children (0.28 $kPa\,L^{-1}\,s$).[12] However, in the latter study, short-term repeatability has been assessed in field conditions whereas in the two former and in the present study, standardized conditions were used. In Beelen et al.'s[12] study long-term Rint repeatability differed according to whether measurements were performed in field conditions or under standardized conditions. This result on long-term reproducibility cannot be readily extrapolated to short-term repeatability, and therefore requires specific investigation. Moreover, in two studies reporting CR for large mixed populations of healthy, asthmatics and coughers the CRs were similar to the CRs of the present study (from 0.15 to 0.21 $kPa\,L^{-1}\,s$).[7,11] Finally, in healthy and asthmatic preschool children, Nielsen et al. using the opening technique (Rint-o), calculated within SD (SDw) of 0.078 $kPa\,L^{-1}\,s$, which corresponded to a Rint CR of 0.16 $kPa\,L^{-1}\,s$.[13] In previous studies, Rint CR has been found to range from 0.15 to 0.25 $kPa\,L^{-1}\,s$ in standardized conditions, i.e., in line with our results.

We did not study Rint change after placebo administration. Previous studies[7,11,13] found no significant Rint change after BD placebo administration. In 55 preschool children, the CR of Rint after placebo inhalation was 0.19 $kPa\,L^{-1}\,s$,[11] within the range of short-term repeatability without any intervention. In another study, the CR of Rint-o after placebo inhalation was 0.25 $kPa\,L^{-1}\,s$.[13] Therefore, placebo administration does not modify Rint short-term repeatability, and does not appear to be mandatory to interpret Rint change after intervention.

Post-bronchodilator changes

Using the same method and device, we have previously demonstrated that the most appropriate BDR cut-off to distinguish asthmatic from healthy preschool children was −35% of predicted.[4] However, the BDR overlap between healthy and sick children complicates its interpretation. Four studies have compared BDR in healthy and in asthmatic subjects, using the Rint technique in school and preschool children,[4,5,7] and Rint-o technique in preschool children.[13] In two studies, the mean Rint decrease in asthmatics was within the limit of BDR in healthy children,[4,13] whereas in the remaining two studies, it was larger than the BDR in healthy children.[5,7] The between-studies difference in BDR in asthmatic children may reflect the heterogeneity of the studied population in terms of age and size of studied populations, level of BDR, anti-asthma medication use, way to express DBR.[18] Furthermore, in one study, a different technique of Rint measurement has been used. However, in two studies, the Rint CR in wheezers did not exceed the magnitude of the BDR cut-off,[7,13] indicating the reliability of cut-offs exceeding the technical and biological variability. In the present study, the Rint CR in asthmatics (32% of predicted) was not larger than the cut-off established in our previous study in healthy and asthmatic children (−35% of predicted).[4]

We did not find any difference between RintB1 and RintB2 measurements. However, the between-test repeatability (CR) was larger than the median post-BD Rint decrease. Therefore, according to the considered baseline Rint value, significance of post-BD Rint varied in 20% of the study children (Figure 2). To the best of our knowledge, no study has previously assessed the influence of Rint short-term repeatability on BDR significance. This result strongly suggests that one single BDR measurement in preschool children with respiratory complains should be considered with caution. In a recent study, different methods to analyze post-occlusion oscillations were used to assess BDR in preschool children and showed a higher sensitivity than the linear back extrapolation method.[19] Therefore, in line with the recently published recommendations,[20] we agree that the linear back extrapolation is the usual algorithm to use for Rint calculation, but that other pressure transient analysis is promising and should be further studied. It will

also be necessary to compare BDR assessed by the classical Rint technique to BDR assessed by specific airway resistance (sRaw). Until now, only Rint-o technique has been compared to sRaw for assessment of BDR in preschool children.[13] The authors reported sensitivity and specificity for Rint-o and sRaw (58% and 70%, and 66% and 81%, respectively), using a larger cut-off for sRaw (−3 SDw) than for Rint-o (−2.5 SDw).

Finally, we did not find any difference in BDR between asthmatics and coughers. These findings confirm the result of Chan et al. but are opposed to those of McKenzie and coworkers[5,7] It is likely that these conflicting results may be due to differences in the way to express BDR.[18]

Conclusion

In this study, Rint short-term repeatability was a median Rint CV of 10–12%, and a CR of 0.16 and 0.25 kPa L^{-1} s, in coughers and asthmatics, respectively. Both indices were unrelated to age, health status, or airway caliber. In asthmatic subjects, the cut-off for a significant post-interventional change in Rint values based on the CR was 0.25 kPa L^{-1} s and 32% of predicted. Thus, the result of Rint repeatability in asthmatics allows to use the previously published cut-off obtained from BDR measurement in asthmatic and healthy preschool children (−35% of predicted). However, BDR significance in individuals did vary, due to Rint variability, in 20% of the tested children. In order to clarify the technical and the biological aspects of Rint short-term variability, further studies including preschool children with different levels of obstruction, should compare (1) Rint to other resistance measurement technique and (2) different methods of calculation of Rint and ways to express BDR.

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