Can Bronchodilator Response Predict Bronchial Response to Methacholine in Preschool Coughers?

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Summary. The aim of the present study was to determine the relationship between bronchodilator response, assessed by interrupter resistance (Rint), and bronchial reactivity in preschool children with chronic cough. Thirty-eight children coughers (median age 5.0 years, range 2.8–6.4) were tested. Bronchodilator response was recorded within 4 months before methacholine challenge. Response to the latter was assessed using transcutaneous partial pressure of oxygen and Rint. Children were considered responders if a 20% fall in transcutaneous partial pressure of oxygen occurred during the bronchial challenge. Bronchodilator response was not different between responders (n = 24) and nonresponders (n = 14) [median (range)] C0.11 (C0.44–0.09) vs. C0.08 (C0.21–0.10) kPa L−1 sec; respectively]. However, none of the nonresponders had a bronchodilator response larger than C0.21 kPa L−1 sec, this cutoff had a 100% positive and a 44% negative predictive value to predict a positive methacholine challenge. The relationship between bronchodilator response and bronchial methacholine responsiveness reached the limit of significance (P = 0.048). Furthermore, the magnitude of the bronchodilator response was correlated to the level of methacholine-induced level of bronchoconstriction (P = 0.01), and to the postchallenge bronchodilation (P = 0.04), all values expressed as % predicted. Moreover, the postbronchodilator Rint value obtained with preceding methacholine challenge was lower than the postbronchodilator value without preceding methacholine challenge in 71.4% (10/14) of the nonresponders and in only 33.3% (8/24) of the responders. Conclusions in preschool coughers bronchodilator response, assessed by the interrupter technique, was correlated to the bronchial responsiveness to methacholine. Non responders had a bronchodilator response not larger than C0.21 kPa L−1 sec.


Key words: bronchial responsiveness; interrupter resistance; transcutaneous partial pressure of oxygen; chronic cough; preschool children.

INTRODUCTION

Bronchodilator response (BDR) and bronchial challenge-induced bronchoconstriction are routinely used in asthmatic patients to guide pharmacological treatment and to assess asthma severity.1,2 Patients with nonspecific respiratory symptoms such as chronic cough, may have a positive BDR or a bronchial hyper-responsiveness to various bronchial stimuli. In that case the possibility of a diagnosis of cough variant of asthma is evoked, and a treatment trial of inhaled corticosteroids is justified. In the diagnosis procedure, the bronchial challenge test is generally not performed if the BDR is positive.3

It would be useful, especially in preschool children in whom pulmonary function testing is time consuming and response to bronchodilator not well established,4 to know if the BDR can predict the bronchial reactivity during bronchial challenge, and avoid the second test. One study in children failed to found any relationship between bronchodilator response and bronchial responsiveness to methacholine challenge (MTC).5 In this study, conducted in coughers and wheezers with suspected asthma, the bronchial responsiveness was assessed by forced expiratory maneuver. The mandatory deep inspiration preceding forced expiratory maneuver may influence the bronchial challenge result, because it induces bronchoconstriction in most asthmatics, and bronchodilation in few asthmatic and in healthy subjects.6 This phenomenon varies with

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age, lacking in infants and being measurable in school children. The interrupter resistance (Rint) is a non-invasive technique that allows respiratory resistance measurement during quiet breathing. Normative values and data on reproducibility of Rint are available. We used Rint technique to assess BDR, in preschool children with chronic cough before a MTC was undertaken. We studied the relationship between BDR and bronchial response to methacholine in preschool children with chronic cough, but no wheeze. Focusing on coughers and using tidal breathing methods to assess bronchial response, we aimed to avoid the unpredictable effect of deep-inspiration in asthmatics.

METHODS

Subjects

We checked for all files of MTC performed in preschool children in our laboratory between April 2001 and May 2007. During this period, in our lab, all children referred for suspicion of asthma with normal baseline Rint, and whatever the magnitude of BDR, were invited to come on a second occasion for MTC. We then looked at the clinical symptoms and excluded children with a diagnosis of asthma. Finally, we selected the children that had had a measurement of BDR within the 4 months preceding the MTC. We found 38 children with chronic non-productive cough, without evidence of any other relevant disease referred twice to the physiology laboratory, a first time for BDR, and a second time for MTC. None of the children used anti asthma medication or had wheezing episodes in the last year, or had a medical diagnosis of asthma. All the study patients had been free from respiratory infection for at least 3 weeks at the time of the tests. A physical examination, including height and weight measurements, was performed on the days of the tests.

Procedures

From 2001, techniques, material and procedures in our laboratory have remained similar to what we have previously published. Briefly, Rint was measured using a Spiroteq apparatus (Dyn'R Ltd, Toulouse, France) and MTC was performed according to the dosimeter method (MB3, Mefar, Bovezzo, Italy) and assessed by transcutaneous oxygen tension (TcPO2) electrode, Radiometer, Copenhagen, Denmark) and Rint measurement. The methacholine challenge was performed only if the TcPO2 pretest value was greater than 75 mm Hg and SaO2 >94%.

The Spiroteq apparatus was calibrated daily for flow, with accuracy of 1%. Rint was measured during expiration for BDR assessment, and during inspiration for methacholine-induced bronchoconstriction detection, using linear-back extrapolation of mouth pressure to estimate alveolar pressure for Rint calculation. Given the long duration of the MTC and the limited patience of preschool children it was not possible to measure both expiratory and inspiratory Rint during the MTC. The conditions and validation of Rint measurements have been described previously. The Rint value was the mean of at least seven validated Rint measurements. We used the mean rather than the median of the interruptions as recently recommended for two reasons. First, the difference between mean and median has been found to do not differ significantly. Secondly, we wished to express Rint values as percentage predicted of the mean of 7 interruptions. The Radiometer apparatus was calibrated just before the bronchial challenge.

Bronchodilator Response

After baseline Rint measurement (RintBD), salbutamol (400 μg) was delivered using a metered-dose inhaler and a spacer (Volumatic, Glaxo, UK), and postbronchodilator Rint (RintBDR) was measured 15 min later.

Methacholine Challenge

The procedure has been previously described. Rint was measured pretest (RintBBD), after saline (baseline) (RintBMT) and after the last dose of methacholine (RintMTC). The methacholine was delivered at intervals no longer than 5 min; therefore the cumulative dose inhaled was 50, 100, 200, 400, and 800 μg. The TcPO2 value was obtained pretest, after 20 min stabilization, then 2–3 min after inhalation of saline (baseline value) and methacholine (challenge value) during stable breathing. The test was stopped when TcPO2 fell by at least 20% versus baseline, or when a cumulative dose of 800 μg of methacholine had been inhaled. If TcPO2 fell by at least 20% during the test, the child was considered as responder. After the final dose of methacholine, and whatever the TcPO2 change, salbutamol (400 μg) was delivered using a metered-dose inhaler and a spacer. Rint was measured 15 min after the inhalation of salbutamol (RintBDMTC) and TcPO2 electrode was removed only when TcPO2 had returned to at least 90% of baseline.

The provocative dose (PD20) in responders was calculated by linear interpolation of the dose (log)—response curve, and a PD of 1,600 μg was attributed to nonresponders.

Statistical Analysis

Data were expressed as frequencies (percentages) for categorical variables and medians (range) for continuous variables. Comparisons between groups used the chi-square or Fisher exact test, as appropriate, for categorical
variables and the Wilcoxon or Wilcoxon matched-pairs signed rank sum test, as appropriate, for continuous variables. Spearman’s rank correlation coefficients were used as nonparametric measure of correlation. All tests were two-tailed, and $P$ values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS 8.2 (SAS, Inc., Cary, NC).

**RESULTS**

**Subjects**

The thirty-eight children were 15 boys and 23 girls, with median (range) age, height, weight, and body mass index (BMI) of 5.0 (2.8–6.4) years, 111 (98–121) cm, 19 (14–29) kg, 15.7 kg m$^{-2}$ (12.2–21); respectively. No children had any anti asthma medication at the time of the tests. Pulmonary auscultation was normal in all children before testing.

**Bronchodilator Response**

Rint measurements at baseline and BDR results, for all the study children, are summarized in Table 1. Before or after bronchodilator administration, none of the study children had a Rint value outside the range of the predicted. As compared to baseline, the group median Rint value was significantly decreased by bronchodilator ($P < 0.0001$), BDR being larger in children with higher Rint$_{BD}$. Neither age, and gender nor BMI did influence the BDR. Five responders had a BDR larger than the previously proposed cutoff of $-0.25$ kPa L$^{-1}$ sec of the predicted, of whom only one had a BDR outside the 95% CI limits for healthy (i.e., larger than $-46\%$) (see also Fig. 2).

**Methacholine Challenge**

The median (and range) of the time interval between BDR and MTC tests was 77 (3–120) days. In order to assess the difference between the pretest Rint on the two occasions (Rint$_{BD}$, and Rint$_{MTC}$), we calculated the coefficient of repeatability of Rint between the two occasions. Rint was measured during expiration for BDR assessment as recommended, and during inspiration during methacholine challenge to minimize the possible interference of laryngeal methacholine response. Since, inspiratory and expiratory Rint cannot be used interchangeably in one subject, and therefore, we could not readily compare absolute values of Rint, we expressed the difference between the two measurements as percentage predicted. The mean (SD) difference between Rint$_{BD}$ and Rint$_{MTC}$ was $-3.9$ (14.3)% of the predicted, which corresponded to a coefficient of repeatability (2 SD of the difference) of 28.6% of the predicted. On the day of the MTC, one child had both Rint$_{MTC}$ and Rint$_{BMTC}$ outside the range of predicted value (152% and 160% of predicted; respectively), and one child had only an increased Rint$_{BMTC}$ (153% of the predicted). The median (range) increase from baseline in Rint during challenge in all the study children was 32.3 ($-20.7$–$-104$)% of the predicted (37.7 ($-3.0$–$-104.1$)% and 25.5 ($-20.7$–$-70.6$)% in responders and nonresponders; respectively). Three non responders coughed during the test. Nine responders had one or more respiratory symptoms during the test: 5 had cough, 4 had dyspnea with tachypnea in 2, 3 wheezed, and one had isolated tachypnea. The respiratory symptoms consistently resolved before or after bronchodilator administration. After bronchodilator administration, Rint$_{BMTC}$ was lower than all baseline values (Rint$_{BD}$, Rint$_{MTC}$, and Rint$_{BMTC}$; $P < 0.0001$), but not significantly different from postbronchodilator Rint measured on the first occasion (Rint$_{BDBD}$). Neither age, and gender nor BMI had any effect on the level of bronchial reactivity.

**Relationship Between BDR and Bronchial Responsiveness**

Rint$_{BD}$ and Rint$_{BDBD}$ values were not different between responders and non responders ($P = 0.63$ and $P = 0.94$; respectively). However, on the first occasion, Rint significantly decreased after bronchodilator in responders ($P < 0.0001$), whereas it did not in non responders ($P = 0.07$). The magnitude of the BDR was not different between responders and non responders (Table 1), and the maximal magnitude of BDR in nonresponders was $-0.21$ kPa L$^{-1}$ sec (Fig. 1). Previously proposed

| TABLE 1 — Bronchodilator Response on First Occasion, in Responders and Nonresponders |
|-----------------------------------------------|----------------|--------------------|
| Rint$_{BD}$ (kPa L$^{-1}$ sec) | 0.86 (0.62–1.15) | 0.87 (0.62–1.15) | 0.73 (0.62–1.10) |
| Rint$_{BD}$ (% predicted) | 103.0 (79.9–143.7) | 109.8 (85.9–143.7) | 96.2 (79.9–127.7) |
| Rint$_{BMTC}$ (kPa L$^{-1}$ sec) | $-0.10$ ($-0.44$–$-0.10$) | $-0.11$ ($-0.44$–$-0.09$) | $-0.08$ ($-0.21$–$-0.10$) |
| Rint$_{BMTC}$ (% predicted) | $-12.8$ ($-57.4$–14.0) | $-13.9$ ($-57.4$–10.9) | $-9.8$ ($-25.1$–14.0) |

Results are medians (range). Rint, interrupter resistance; baseline Rint (Rint$_{BD}$), Rint before bronchodilator administration; BDR, bronchodilator response, that is, the difference between after and before bronchodilator administration Rint measurements.

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−0.25 kPa L\(^{-1}\) sec cutoff\(^{12,14}\) and the present −0.21 kPa L\(^{-1}\) sec limit, gave similar positive and negative predictive values (PPV and NPV) to predict a positive MTC, that is, 100% PPV and 42% and 44% NPV; respectively.

The relationship between absolute BDR and bronchial responsiveness is shown in Figure 2. The relationship was similar when BDR was expressed in percentage predicted (data not shown). Without taking into account the outlier (Fig. 2), the relationship between BDR and bronchial responsiveness reached the limit of significance (\(P = 0.048, r = 0.33\)). BDR was correlated to the level of methacholine-induced level of bronchoconstriction (Rint\(_{MTC}\)) (\(P = 0.008; r = −0.42\) for absolutes values (Fig. 3), and \(P = 0.02; r = −0.36\) for % predicted), and to the postbronchodilator Rint decrease after challenge (Rint\(_{BD,MTC}\) minus Rint\(_{BD,TC}\)) (\(P = 0.037; r = 0.34\) for absolute value, and \(P = 0.02; r = 0.39\) for % predicted).

Finally, the Rint\(_{BD,MTC}\) was lower than Rint\(_{BD,BD}\), both expressed as percentage of predicted, in 8 (33.3%) of the responders, and in 10 (71.4%) of the nonresponders.

DISCUSSION

In all, except one, of the 38 preschool children with chronic cough, we found that BDR correlated with bronchial methacholine responsiveness. The details of our results are in favor of multiple mechanisms influencing bronchial responsiveness. Health status, as well as techniques of lung function measurement, are important to take into account in the interpretation of data of bronchial responsiveness.

Subjects

Asthma is a clinical condition that is often associated with bronchial hyperresponsiveness.\(^2\) In the present study, preschool children with suspected asthma were referred to the laboratory for bronchial responsiveness assessment, in order to help in the diagnosis of their respiratory disorder. We included children with chronic cough but no current wheezy episodes and no medical diagnosis of asthma. Thereby, we were able to study preschool children using no anti asthma medication. Indeed, wheezy and asthmatic children are prone to use inhaled corticosteroids that modify bronchial reactivity.\(^{15,16}\) Bibi et al.\(^5\) stated that the use of inhaled corticosteroids in a number, but not all of their study children, may partly explain the weak correlation they found between BDR and bronchial reactivity in children.
Measurement Conditions

Because of the retrospective nature of the study, the time interval between BDR and bronchial challenge tests was not controlled. However, we decided to keep the interval less than 4 months to avoid large season variation, and it is to be noted that the clinical symptoms did not vary between the two occasions. We also checked that the children were free of any recent respiratory infection or current medication.4 Another potential bias was the possible change in baseline lung function between the two occasions. To document the reproducibility of the pretest Rint, we calculated the coefficient of repeatability that reflected the long term variability of the Rint measurement in our study children. The coefficient of repeatability between the two occasions (28.6%) was similar to previous published data in healthy (32%).17 Therefore, children were tested in similar clinical and functional baseline conditions, taking into account the long term variability of the Rint technique in healthy preschool children. Finally, as the variability of bronchial hyper-responsiveness has not been studied in preschool children with chronic cough, we cannot exclude that the long interval between the two tests might have affected the results of the present study.

Relationship Between Bronchodilator Response and Bronchial Reactivity

Although, there was no difference in BDR between responders and non responders, Figure 1 illustrates the narrower range of BDR in the nonresponder group compared to that of the responder group. This result is inline with Bibi et al.5 study that showed a maximal 6% change in FEV1 after bronchodilator administration, in non responders suspected of asthma or healthy. It has to be noted that the maximal BDR in non responders (i.e., −0.21 kPa·L\(^{-1}\)·sec\(^{-1}\)) was close to the short-term Rint repeatability we and others have calculated in preschool children with cough or healthy, tested in standardized conditions (from 0.17 to 0.25 kPa·L\(^{-1}\)·sec\(^{-1}\)).12,17–19 We, therefore, submit the view that preschool coughers with a BDR larger than the short term repeatability had a true Rint change after bronchodilator administration which predicted bronchial hyperresponsiveness to MTC (PPV 100%). In contrast, preschool coughers with a BDR within the limits of the short term repeatability cannot be considered to have a true Rint change and may or may not have bronchial hyperresponsiveness (NPV 44%). However, since the present study included only five children with a significant BDR, these results have to be confirmed in a specific study in children with positive BDR.

Bronchial reactivity to MTC was assessed using the TcPO\(_2\) technique. This technique has been safely used in healthy and sick preschool and school age children, and in adults with no side effects and a good repeatability.22 This technique does not involve forced expiratory maneuver and is, therefore, particularly convenient in preschool children testing. In children with cough or wheeze, able to perform repeated forced expiratory curves, Bibi et al.5 did not find any significant relationship between bronchial responses to bronchodilator and to methacholine. However, FEV1 measurement is modified by the variable effect of deep-inspiration on airway diameter. Deep-inspiration may result in bronchoconstriction that can last 1–2 min in asthmatic patients.23 The deep-inspiration may increase bronchial challenge responsiveness especially in asthmatics,24 whereas it has a bronchoprotective effect in healthy,25 and also in some asthmatics.26 Other phenomenons such as a decrease in intrapulmonary methacholine deposition with the dosimeter method, the thickness of smooth muscle layer, and the modification of bronchial geometry, can modify to an unpredictable degree, the level of bronchial responsiveness in asthmatics. In these patients, the relationship between BDR and bronchial challenge responsiveness may be under many influences that vary according to the level of asthma severity, and the amount of anti asthma medication. In our study including preschool children with cough and using a lung function techniques that did not involve deep-inspiration, we may have studied a relationship between BDR and bronchial responsiveness to MTC without potential confounders. While the techniques we used to assess bronchial responsiveness did not rely on deep-inspiration, the inhalation of methacholine did required deep-inspiration. However, we recorded TcPO\(_2\) 2–3 min after methacholine inhalation, a time at which the possible deep-inspiration induced bronchoconstriction was no longer present,23 but the methacholine induced bronchoconstriction still present.25 The correlation between BDR and bronchial challenge responsiveness found in our study is inline with a study conducted in mice (in vitro) and in healthy adults, where the level of bronchial basal tone was related to the bronchial hyper-responsiveness.27 Interestingly, the only child with a BDR outside the limits of normal had a bronchial reactivity outside the significant relationship disclosed in all the other study children (Fig. 2), in favor of distinct bronchial responsiveness patterns in asthmatic and in non asthmatic preschool children. However, due to the study design, we cannot exclude that the time interval between the two tests might have influenced this result.

Bronchodilator Response With and Without Preceding Methacholine Challenge

The BDR measured, in our study children, was similar to that of healthy preschool children,14 suggesting that there were virtually no asthmatics in our population. No recommendations for a positive BDR using the Rint
technique are currently available, and we did not select children with respect to the magnitude of the BDR on first occasion. However, with respect to the overlap between BDR in asthmatic and in healthy preschool children, we have proposed and validated a cutoff of $-0.25$ kPa $L^{-1} s$ sec ($-35\%$ of the predicted).$^{12,14}$ None of the non responders, and only five responders had an absolute BDR larger than this cutoff. Since, in our study, BDR was not affected by any anti asthma medication use, we believe that we did not study many asthmatic children.

We also looked at the postbronchodilator Rint on the two occasions and found that in some children $\text{RintBD}_{MTC}$ ($\%$ predicted) was lower than $\text{RintBD}_{BD}$ ($\%$ predicted). While this difference was detected in most of the nonresponders ($71.4\%$), it was present in only $33.3\%$ of the responders. In a study conducted in asthmatic children, Kamps et al.$^{28}$ showed a smaller BDR expressed as mean (SD) percentage of FEV1, with than without preceding MTC ($5.2$ ($1.5\%$) and $10.4$ ($1.4\%$); respectively). Furthermore, an in vitro study on adult guinea pigs showed that airway smooth muscle level of tension after a maximal contraction varied according to baseline tone.$^{29}$ Taken together, these results suggest that baseline airway tone may influence the subsequent BDR. Further studies are needed to establish if there is an opposite effect of the basal bronchial tone and/or of the level of bronchoconstriction, on the magnitude of postchallenge bronchial relaxation, in responders and nonresponders.

On the other hand, it has been shown that during bronchial challenge in asthmatic adult$^{30}$ and children,$^{31}$ bronchodilator administered after FEV1 had spontaneously returned to baseline (i.e., after $30–90$ min) resulted in a BDR similar to the BDR measured without preceding bronchial challenge. These two studies together with the study of Kamps et al.$^{28}$ are in favor of a non exclusive airway smooth muscle-related bronchial response during bronchial challenge and postchallenge BDR. Oedema of the tracheobronchial mucosa is a consequence of increased vascular permeability that occurs during bronchial challenge, particularly in asthmatics.$^{32,33}$ It is likely that no or less vascular modifications occurred in our nonresponders, consistent with a more frequent $\text{RintBD}_{MTC} < \text{RintBD}_{BD}$ in non responders than in responders. This result supports the possibility that smooth muscle contraction was the main mechanism of the Rint increase during methacholine challenge in nonresponders, where oedema of the airway might have played a more important role in responders.

Finally, the last point of the discussion is the dose of bronchodilator we administered. In most studies in preschool and school age children, a lower or equal dose of bronchodilator was administered after pharmacological bronchial challenge$^{34–36}$ than that used in the present study. However, Merkus et al.$^{31}$ demonstrated, in asthmatic children, that after MTC and spontaneous return to baseline FEV1, the administration of $800 \mu g$ of inhaled salbutamol resulted in a larger BDR than a $400 \mu g$ dose. We did not wait for spontaneous recovering of the bronchoconstriction and administered $400 \mu g$ of salbutamol immediately after bronchial challenge. In Kamps et al.$^{28}$ study, $800 \mu g$ of salbutamol administered immediately after MTC in asthmatic children, failed to provoke a BDR as large as the BDR obtained without preceding MTC. Therefore, we feel that the timing of the bronchodilator administration was more important than the delivered dose. Thus, if our result in coughers can be extrapolated from that in asthmatic children, a higher dose of bronchodilator would not have modified the BDR we measured.

In conclusion, using pulmonary function tests that avoided deep-inspiration in preschool children with chronic cough, we found a correlation between BDR and bronchial responsiveness to methacholine. In the present study, a BDR larger than $-0.21$ kPa $L^{-1} s$, that is, similar to the Rint short term repeatability, had a $100\%$ PPV and a $44\%$ NPV to predict a positive MTC. However, it is likely that our result cannot be readily extrapolated to asthmatic preschool children, because of possible different underlying mechanisms of bronchial responsiveness.

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