Interrupter resistance and oxygen saturation for methacholine challenge in young children

To the Editor:

In young children unable to perform reliable and reproducible spirometry, non-cooperative lung function techniques are necessary to measure bronchial hyperreactivity (BHR) during bronchial challenge [1]. Measuring the decrease in transcutaneous partial pressure of oxygen (PtcO2) is a robust technique that detects increased ventilation–perfusion mismatch during bronchial challenge [2] in preschool and school-aged children [3–5], and a 20% decrease in PtcO2 correlates to a 20% forced expiratory volume in 1 s (FEV1) decrease in children aged 6–14 years [3] and in adults (with correlation to arterial oxygen tension) [6]. When neither spirometry nor PtcO2 is available, other BHR outcomes can be measured such as wheezing that appears for mean±SD decreases of −44.7±14.5% in FEV1 and −6.3±2.7% in transcutaneous saturation of oxygen (SpO2) [7]. Respiratory resistances are easy to measure [8–10] but the relevant threshold for BHR is not yet defined and an at least 35% increase variably correlates with PtcO2 changes [8, 11]. First, we aimed to better study two alternative outcomes (i.e. interrupter resistance (Rint) and SpO2) and challenge the current recommendations [1] of measuring resistance during inspiration (as opposed to measuring during expiration for reversibility testing [12]), because the physiological expiratory glottis closure can be enhanced during bronchial challenge-induced bronchoconstriction and specific extrathoracic airway reactivity to bronchoconstrictor agents can occur. Second, we wished to evaluate the proposed thresholds for Rint and SpO2 (+35% and −5% baseline, respectively), as only a 3% decrease is considered to be significant in sleep studies and a mean±SD SpO2 decrease of −5.2±3.1% corresponds to a much larger than 20% decrease in FEV1 in 5–8-year-old asthmatic children [−33.3±7.4% decrease in FEV1] [13].

Between June 2013 and September 2014, we prospectively and consecutively included 28 children unable to correctly perform a spirometry who were referred to our lung function laboratory for a methacholine challenge. Children had to be free of treatment and acute respiratory symptoms for 3 weeks. Chest auscultation had to be normal.

At each step of the bronchial challenge, inspiratory and expiratory series of at least five correct interruptions (Rint_insp and Rint_exp, respectively) were performed in random order (but always in the same order with each specific child) using a MicroRint device (Micro Medical, Rochester, UK). PtcO2 and SpO2 were recorded throughout the test as previously described [8] using a Tina CombiM (Radiometer, Bronshoj, Denmark). Lung function was checked to be within the range of normal at baseline and assessed after inhalation of saline (diluent) to obtain the reference for changes during the challenge. Doubling doses of methacholine were inhaled, using the dosimeter method, every 5 min [8], from 50 µg up to a cumulative dose of 800 µg. The test ended when PtcO2 had fallen by 20% or more (PD20PtcO2), the child had respiratory symptoms or the maximal dose of methacholine was reached. The study was approved by the Institutional Review Board of the French learned society for respiratory medicine (Société de Pneumologie de Langue Française) (CEPRO 2013-015) and the children’s parents gave informed consent to the study.

Repeated measurements in children were compared using paired the Wilcoxon signed-rank test. Comparisons of lung function indices between groups of children (responsive and nonresponsive) were performed using the Fisher exact test.

27 (13 girls and 14 boys, median (range) age 5.5 (4.2–8.1) years) children completed all measurements during the bronchial challenge. One child pulled off the PtcO2 electrode before the end of the test and was, therefore, excluded. 25 children were referred for chronic cough (started at a median age of 2.7 (0.3–8) years), one for suspicion of wheezing and one for dyspnoea upon exertion.

At baseline, Rint_insp was higher than Rint_exp (mean 0.81 versus 0.60 kPa·s·L−1, with a mean difference of −0.21 kPa·s·L−1 (95% CI −0.26 to −0.16 kPa·s·L−1); p<0.0001), but within the range of normal for all children [14]. At the time of interruption, expiratory airflow was lower than inspiratory airflow throughout the test (e.g. at baseline: 0.30 and 0.39 L·s−1, respectively; p<0.002). 20 children reached the PD20PtcO2 at a median cumulative dose of methacholine of 100 µg (50–400 µg) (responsive children) without any respiratory symptoms. 14 responsive children had an at least 35% Rint_insp increase (PD35Rint_insp) during the methacholine
challenge whereas six responsive children and all the nonresponsive children did not reach PD35Rint
(p<0.002). Using Rint, there was no association between PD35Rint at any time during the test and the
presence of BHR (p=1). Therefore, sensitivity and specificity were 70% (95% CI 48–85%) and 100% (95% CI
65–100%), respectively; for Rint, and 50% (95% CI 30–70%) and 57% (95% CI 25–84%), respectively, for
Rint, to detect BHR at or before PD20Pco2. Taking into account all cases of discordance between Rint
and Pco2 changes (significance of the changes at each test step), the number of discordant Rint values (n=19)
was higher than that of Rint values (n=11) (table 1). For both Rint measurements, the discordances with
Pco2 changes were equally due to PD35Rint reached before PD20Pco2 or to a less than 35% Rint increase at
PD20Pco2. In the majority of cases, Rint steadily increased during the bronchial challenge, whereas Rint
had a more irregular pattern of changes and the final change in Rint was smaller than that of Rint in all
the study children (table 1). All the children (n=11) whose Rint increased by 35% or more without a
concomitant 20% Pco2 decrease were eventually responsive, whereas three of the nine children with early
PD35Rint remained nonresponsive throughout the test (three Rint false positives). Finally, at PD20Pco2,
Rint and Rint would not have diagnosed BHR in six cases and 10 cases, respectively (false negative),
representing 12 children, among whom only two had a 3% decrease in SpO2 at the same time.

Using Rint changes expressed as percentage of predicted rather than percentage of baseline would have
changed the significance of a Rint increase in two out of 81 Rint measurements performed after methacholine
inhalation in all study children. These two measurements occurred after the first dose of methacholine in
two discordant children (PD35Rint reached before PD20Pco2) in whom, after the second methacholine
inhalation, both changes (% predicted and % baseline) corresponded but remained discordant with that of
PD20Pco2. Therefore, the analysis of the concordance between Rint and PD20Pco2 changes would not change
using percentage predicted or percentage baseline.

If the threshold for Rint were increased by up to 40%, discordance between Pco2 and Rint would remain
the same, whereas discordance with Rint would decrease from 19 to 15 cases (still with two false
positives). If a 3% decrease in SpO2 were the threshold, 15 out of the 20 responsive children would have
reached this threshold at PD20Pco2 (none before PD20Pco2), while none of the nonresponsive children
would have reached it at any step of the test (p<0.001). Moreover, using PD35Rint or a 3% decrease in
SpO2 as a composite criterion for bronchial responsiveness, only one responsive child would not have been
diagnosed as responsive at PD20Pco2 (sensitivity 95%, 95% CI 76–99%) versus six false negatives with
PD35Rint or <5% SpO2 criterion.

**Table 1: Changes and discordances during methacholine challenge between interrupter
resistance [Rint] and transcutaneous partial pressure of oxygen [Pco2].**

| Subjects n | Responsive children | Nonresponsive children |
|------------|---------------------|------------------------|
| Changes in Pco2 % | −25.4±4.8 | −13.4±8.4 |
| Changes Rint % | +49.1±29.6 | +13.2±11.4 |
| Change Rint % | +34.3±27.9 | +8.8±17.4 |
| Discordance between Rint and Pco2 n (%), 95% CI | 11 [55, 34–74] | 0 [0, 0–35] |
| Rint increase <35% at PD20Pco2 n | 6 | |
| Rint increase ≥35% before PD20Pco2 n | 5 | |
| Discordance between PD35Rint+SpO23% and Pco2 n | 6 | 0 |

Data are presented as mean± standard deviation of post-diluent values unless otherwise stated. Changes are at
the provocative dose of methacholine causing a 20% decrease in Pco2 [PD20Pco2] in responsive children
and at the last dose of methacholine in nonresponsive children. Discordances between Rint and Pco2
changes were assessed at every step of the test. Rint changes are more or less than 35% increase from
the post-diluent value [PD35Rint]. Rint: inspiratory interrupter resistance; Rint: expiratory interrupter
resistance; PD35Rint: provocative dose of methacholine causing a 35% decrease in Rint; SpO2; at least
3% decrease in transcutaneous saturation of oxygen from the post-diluent value; PD35Rint: provocative
dose of methacholine causing a 35% decrease in Rint.
Our results do not support a universal physiological mechanism to explain discrepancies between $R_{int}$ and $P_{tcO2}$ measurements during bronchial challenge in young children. The lack of $R_{int}$ increase in responsive children could reflect an early ventilation–perfusion mismatch with no central airway obstruction but the better concordance between $P_{tcO2}$ and $R_{int}$ only over $R_{int}$ remains unexplained. The early reactivity in $R_{int}$ (before $PD_{20}P_{tcO2}$) might be due to glottis changes but we failed to demonstrate any specific recurring patterns of changes of airflow at interruption or of difference between $R_{int}$ and $R_{int}$ explaining the discrepancies recorded.

To challenge the proposed threshold for $R_{int}$ [1], we switched from a 35% to a 40% increase and the total number of discordances decreased only for $R_{int}$ although they remained higher than that of $R_{intexp}$. However, as a $R_{int}$ device may measure only $R_{int}$, the threshold of 40% may be useful to implement. In children with no $R_{int}$ increase at $PD_{20}P_{tcO2}$, a 3% decrease in $SpO2$ better detected BHR than a 5% decrease. The better accuracy of a $−3\%SpO2$ threshold, over a $−5\%$ threshold, increases the safety of associating $R_{int}$ and $SpO2$ measurements when $P_{tcO2}$ is not available.

In conclusion, $R_{int}$ better detects BHR than $R_{intexp}$ and might better match $PD_{20}P_{tcO2}$ changes. Until larger studies confirm these first results, it is reasonable to stick to the proposal of favouring measurement of $R_{int}$ rather than $R_{intexp}$ during methacholine challenge. Our findings strengthen the recommendation to associate bronchial reactivity outcomes when $P_{tcO2}$ measurement is not available. Finally, the combination of a 35% $R_{int}$ increase or a 3% $SpO2$ decrease might be a useful criterion for detecting BHR with respect to $P_{tcO2}$ changes.

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References

1 Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med 2007; 175: 1304–1345.
2 Hedlin G, Freyschuss U, Hedenstierna G. Histamine-induced asthma in children: effects on the ventilation–perfusion relationship. Clin Physiol 1985; 5: 19–34.
3 van Broekhoven P, Hop WC, Rasser E, et al. Comparison of FEV1 and transcutaneous oxygen tension in the measurement of airway responsiveness to methacholine. Pediatr Pulmonol 1991; 11: 254–258.
4 Holmgren D, Engstrom I, Bjure J, et al. Respiratory resistance and transcutaneous $Po2$ during histamine provocation with bronchial asthma. Pediatr Pulmonol 1993; 15: 168–174.
5 Holmgren D, Redfors S, Wennergren G, et al. Histamine provocation in young, awake children with bronchial asthma; using a fall in oxygenation as the only indicator of a bronchial reaction. Acta Paediatr 1999; 88: 545–549.
6 Dal Negro R, Allegra L. Blood gas changes during and after non specific airway challenge in asthmatic adults and normal subjects. J Appl Physiol 1989; 67: 2627–2630.
7 Bentur I, Beck R, Elias N, et al. Methacholine bronchial provocation measured by spirometry versus wheeze detection in preschool children. BMC Pediatr 2005; 5: 19.
8 Beydon N, Trang-Pham H, Bernard A, et al. Measurements of resistance by the interrupter technique and of transcutaneous partial pressure of oxygen in young children during methacholine challenge. Pediatr Pulmonol 2001; 31: 238–246.
9 Phagoo SB, Wilson NM, Silverman M. Evaluation of the interrupter technique for measuring change in airway resistance in 5-year-old asthmatic children. Pediatr Pulmonol 1995; 20: 387–395.
10 Kivastik J, Talts J, Primhak RA. Interrupter technique and pressure oscillation analysis during bronchoconstriction in children. Clin Physiol Funct Imaging 2009; 29: 43–52.
11 Wilson NM, Bridge P, Phagoo SB, et al. The measurement of methacholine responsiveness in 5 year old children: three methods compared. Eur Respir J 1995; 8: 364–370.
12 Ioan I, Coutier L, Bonabel C, et al. Bronchial obstruction and reversibility in children: inspiratory or expiratory resistance? Eur Respir J 2014; 44: 244–247.
13 Noviski N, Cohen L, Springer C, et al. Bronchial provocation determined by breath sounds compared with lung function. Arch Dis Child 1991; 66: 952–955.
14 Merkus PJ, Stocks J, Beydon N, et al. Reference ranges for interrupter resistance technique: the Asthma UK Initiative. Eur Respir J 2010; 36: 157–163.