



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 (P_{tCO_2}) 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 P_{tCO_2} 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 P_{tCO_2} is available, other BHR outcomes can be measured such as wheezing that appears for mean±SD decreases of $-44.7\pm 14.5\%$ in FEV₁ and $-6.3\pm 2.7\%$ in transcutaneous saturation of oxygen (SpO_2) [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 P_{tCO_2} changes [8, 11]. First, we aimed to better study two alternative outcomes (*i.e.* interrupter resistance (R_{int}) and SpO_2) 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 R_{int} and SpO_2 (+35% and -5% baseline, respectively), as only a 3% decrease is considered to be significant in sleep studies and a mean±SD SpO_2 decrease of $-5.2\pm 3.1\%$ corresponds to a much larger than 20% decrease in FEV₁ in 5–8-year-old asthmatic children ($-33.3\pm 7.4\%$ 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 ($R_{int_{insp}}$ and $R_{int_{exp}}$, respectively) were performed in random order (but always in the same order with each specific child) using a MicroRint device (Micro Medical, Rochester, UK). P_{tCO_2} and SpO_2 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 P_{tCO_2} had fallen by 20% or more (PD₂₀ P_{tCO_2}), 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 P_{tCO_2} 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, $R_{int_{exp}}$ was higher than $R_{int_{insp}}$ (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 – -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 PD₂₀ P_{tCO_2} 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% $R_{int_{insp}}$ increase (PD₃₅ $R_{int_{insp}}$) during the methacholine



challenge whereas six responsive children and all the nonresponsive children did not reach PD35Rint_{insp} ($p < 0.002$). Using Rint_{exp}, there was no association between PD35Rint_{exp} 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_{insp}, and 50% (95% CI 30–70%) and 57% (95% CI 25–84%), respectively, for Rint_{exp} to detect BHR at or before PD20PtcO₂. Taking into account all cases of discordance between Rint and PtcO₂ changes (significance of the changes at each test step), the number of discordant Rint_{exp} values ($n = 19$) was higher than that of Rint_{insp} values ($n = 11$) (table 1). For both Rint measurements, the discordances with PtcO₂ changes were equally due to PD35Rint reached before PD20PtcO₂ or to a less than 35% Rint increase at PD20PtcO₂. In the majority of cases, Rint_{insp} steadily increased during the bronchial challenge, whereas Rint_{exp} had a more irregular pattern of changes and the final change in Rint_{exp} was smaller than that of Rint_{insp} in all the study children (table 1). All the children ($n = 11$) whose Rint_{insp} increased by 35% or more without a concomitant 20% PtcO₂ decrease were eventually responsive, whereas three of the nine children with early PD35Rint_{exp} remained nonresponsive throughout the test (three Rint_{exp} false positives). Finally, at PD20PtcO₂, Rint_{insp} and Rint_{exp} would not have diagnosed BHR in six cases and 10 cases, respectively (false negative), representing 12 children, among whom only two had a 5% decrease in SpO₂ at the same time.

Using Rint_{insp} changes expressed as percentage of predicted rather than percentage of baseline would have changed the significance of a Rint_{insp} increase in two out of 81 Rint_{insp} measurements performed after methacholine inhalation in all study children. These two measurements occurred after the first dose of methacholine in two discordant children (PD35Rint_{insp} reached before PD20PtcO₂) in whom, after the second methacholine inhalation, both changes (% predicted and % baseline) corresponded but remained discordant with that of PD20PtcO₂. Therefore, the analysis of the concordance between Rint_{insp} and PD20PtcO₂ changes would not change using percentage predicted or percentage baseline.

If the threshold for Rint were increased by up to 40%, discordance between PtcO₂ and Rint_{insp} would remain the same, whereas discordance with Rint_{exp} 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 PD20PtcO₂ (none before PD20PtcO₂), while none of the nonresponsive children would have reached it at any step of the test ($p < 0.001$). Moreover, using PD35Rint_{insp} 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 PD20PtcO₂ (sensitivity 95%, 95% CI 76–99%) versus six false negatives with PD35Rint_{insp} or –5% SpO₂ criterion.

TABLE 1 Changes and discordances during methacholine challenge between interrupter resistance (Rint) and transcutaneous partial pressure of oxygen (PtcO₂)

	Responsive children	Nonresponsive children
Subjects n	20	7
Changes in PtcO₂ %	–25.4±4.8	–13.4±8.4
Changes Rint_{insp} %	+49.1±29.6	+13.2±11.4
Change Rint_{exp} %	+34.3±27.9	+8.8±17.4
Discordance between Rint_{insp} and PtcO₂ n (% , 95% CI)	11 (55, 34–74)	0 (0, 0–35)
Rint increase <35% at PD20PtcO ₂ n	6	
Rint increase ≥35% before PD20PtcO ₂ n	5	
Discordance between PD35Rint_{insp}+SpO_{2,3%} and PtcO₂ n	6	0
Discordance between Rint_{exp} and PtcO₂ n (% , 95% CI)	16 (80, 58–92)	3 (42, 16–75)
Rint increase <35% at PD20PtcO ₂ n	10	0
Rint increase ≥35% before PD20PtcO ₂ n	6	3
Discordance between PD35Rint_{exp}+ SpO_{2,3%} and PtcO₂ n	9	3

Data are presented as mean±SD percentage of post-diluent values unless otherwise stated. Changes are at the provocative dose of methacholine causing a 20% decrease in PtcO₂ (PD20PtcO₂) in responsive children and at the last dose of methacholine in nonresponsive children. Discordances between Rint and PtcO₂ changes were assessed at every steps of the test. Rint changes are more or less than 35% increase from the post-diluent value (PD35Rint). Rint_{insp}: inspiratory interrupter resistance; Rint_{exp}: expiratory interrupter resistance; PD35Rint_{insp}: provocative dose of methacholine causing a 35% decrease in Rint_{insp}; SpO_{2,3%}: at least 3% decrease in transcutaneous saturation of oxygen from the post-diluent value; PD35Rint_{exp}: provocative dose of methacholine causing a 35% decrease in Rint_{exp}.

Our results do not support a universal physiological mechanism to explain discrepancies between R_{int} and P_{tCO_2} 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_{tCO_2} and $R_{int_{insp}}$ over $R_{int_{exp}}$ remains unexplained. The early reactivity in R_{int} (before PD20 P_{tCO_2}) 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 $R_{int_{insp}}$ and $R_{int_{exp}}$ 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 $R_{int_{exp}}$ although they remained higher than that of $R_{int_{insp}}$. However, as a R_{int} device may measure only $R_{int_{exp}}$, the threshold of 40% may be useful to implement. In children with no R_{int} increase at PD20 P_{tCO_2} , a 3% decrease in S_{pO_2} better detected BHR than a 5% decrease. The better accuracy of a –3% S_{pO_2} threshold, over a –5% threshold, increases the safety of associating R_{int} and S_{pO_2} measurements when P_{tCO_2} is not available.

In conclusion, $R_{int_{insp}}$ better detects BHR than $R_{int_{exp}}$ and might better match PD20 P_{tCO_2} changes. Until larger studies confirm these first results, it is reasonable to stick to the proposal of favouring measurement of $R_{int_{insp}}$ rather than $R_{int_{exp}}$ during methacholine challenge. Our findings strengthen the recommendation to associate bronchial reactivity outcomes when P_{tCO_2} measurement is not available. Finally, the combination of a 35% $R_{int_{insp}}$ increase or a 3% S_{pO_2} decrease might be a useful criterion for detecting BHR with respect to P_{tCO_2} changes.

Nicole Beydon^{1,2} and Iulia Marian¹

¹APHP, Unité Fonctionnelle de Physiologie-Explorations Fonctionnelles Respiratoires (EFR), Hôpital d'Enfants Armand-Trousseau, Paris, France. ²INSERM U938, Centre de Recherche Saint Antoine, Paris, France.

Correspondence: Nicole Beydon, EFR, Hôpital Armand-Trousseau, 26 Avenue du Docteur Arnold Netter, 75571 Paris, Cedex 12, France. E-mail: nicole.beydon@trs.aphp.fr

Received: May 11 2015 | Accepted after revision: Oct 11 2015

Acknowledgments: We are grateful to Michèle Boulé, Houda Guillo, Marc Koskas, Marie-Claude La Rocca, Lucia Maingot and Noria Medjahdi for their help in recruiting the children, and to Claire Goaugen, Pascal Jacquemart, Valérie Le Bail, Isabelle Schmit and Françoise Vallée (APHP, hôpital Armand Trousseau, Paris, France) for technical assistance. We thank Corinne Alberti (Robert Debré Hospital, Paris, France) for her help with the statistical analysis and Evan Knight for his help in preparing this manuscript.

Conflict of interest: None declared.



@ERSpublications

Inspiratory R_{int} better detects BHR than expiratory R_{int} and might better match PD20 P_{tCO_2} changes <http://ow.ly/TrMvB>

Copyright ©ERS 2015. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

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 PO_2 during histamine provocation in children 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 L, 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: 45–52.
- 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.