ORIGINAL RESEARCH LETTER

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 (FEV_1) 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±14.5% in FEV_1 and −6.3±2.7% in transcutaneous saturation of oxygen (S_{pO_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 S_{pO_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 S_{pO_2} (+35% and −5% baseline, respectively), as only a 3% decrease is considered to be significant in sleep studies and a mean±SD S_{pO_2} decrease of −5.2±3.1% corresponds to a much larger than 20% decrease in FEV_1 in 5–8-year-old asthmatic children (−33.3±7.4% decrease in FEV_1) [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 S_{pO_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 ($PD_{20}P_{tcO_2}$), 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 $kPa{\cdot}s{\cdot}L^{-1}$, with a mean difference of −0.21 $kPa{\cdot}s{\cdot}L^{-1}$ (95% CI −0.26– −0.16 $kPa{\cdot}s{\cdot}L^{-1}$); 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 $L{\cdot}s^{-1}$, respectively; p<0.002). 20 children reached the $PD_{20}P_{tcO_2}$ 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 ($PD_{35}R_{int_{insp}}$) during the methacholine

challenge whereas six responsive children and all the nonresponsive children did not reach $PD_{35}R_{int_{insp}}$ ($p<0.002$). Using $R_{int_{exp}}$, there was no association between $PD_{35}R_{int_{exp}}$ 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 $R_{int_{insp}}$, and 50% (95% CI 30–70%) and 57% (95% CI 25–84%), respectively, for $R_{int_{exp}}$ to detect BHR at or before $PD_{20}P_{tcO_2}$. Taking into account all cases of discordance between R_{int} and P_{tcO_2} changes (significance of the changes at each test step), the number of discordant $R_{int_{exp}}$ values (n=19) was higher than that of $R_{int_{insp}}$ values (n=11) (table 1). For both R_{int} measurements, the discordances with P_{tcO_2} changes were equally due to $PD_{35}R_{int}$ reached before $PD_{20}P_{tcO_2}$ or to a less than 35% R_{int} increase at $PD_{20}P_{tcO_2}$. In the majority of cases, $R_{int_{insp}}$ steadily increased during the bronchial challenge, whereas $R_{int_{exp}}$ had a more irregular pattern of changes and the final change in $R_{int_{exp}}$ was smaller than that of $R_{int_{insp}}$ in all the study children (table 1). All the children (n=11) whose $R_{int_{insp}}$ increased by 35% or more without a concomitant 20% P_{tcO_2} decrease were eventually responsive, whereas three of the nine children with early $PD_{35}R_{int_{exp}}$ remained nonresponsive throughout the test (three $R_{int_{exp}}$ false positives). Finally, at $PD_{20}P_{tcO_2}$, $R_{int_{insp}}$ and $R_{int_{exp}}$ 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 S_{pO_2} at the same time.

Using $R_{int_{insp}}$ changes expressed as percentage of predicted rather than percentage of baseline would have changed the significance of a $R_{int_{insp}}$ increase in two out of 81 $R_{int_{insp}}$ measurements performed after methacholine inhalation in all study children. These two measurements occurred after the first dose of methacholine in two discordant children ($PD_{35}R_{int_{insp}}$ reached before $PD_{20}P_{tcO_2}$) in whom, after the second methacholine inhalation, both changes (% predicted and % baseline) corresponded but remained discordant with that of $PD_{20}P_{tcO_2}$. Therefore, the analysis of the concordance between $R_{int_{insp}}$ and $PD_{20}P_{tcO_2}$ changes would not change using percentage predicted or percentage baseline.

If the threshold for R_{int} were increased by up to 40%, discordance between P_{tcO_2} and $R_{int_{insp}}$ would remain the same, whereas discordance with $R_{int_{exp}}$ would decrease from 19 to 15 cases (still with two false positives). If a 3% decrease in S_{pO_2} were the threshold, 15 out of the 20 responsive children would have reached this threshold at $PD_{20}P_{tcO_2}$ (none before $PD_{20}P_{tcO_2}$), while none of the nonresponsive children would have reached it at any step of the test ($p<0.001$). Moreover, using $PD_{35}R_{int_{insp}}$ or a 3% decrease in S_{pO_2} as a composite criterion for bronchial responsiveness, only one responsive child would not have been diagnosed as responsive at $PD_{20}P_{tcO_2}$ (sensitivity 95%, 95% CI 76–99%) *versus* six false negatives with $PD_{35}R_{int_{insp}}$ or −5% S_{pO_2} criterion.

TABLE 1 Changes and discordances during methacholine challenge between interrupter resistance (R_{int}) and transcutaneous partial pressure of oxygen (P_{tcO_2})

	Responsive children	Nonresponsive children
Subjects n	20	7
Changes in P_{tcO_2} %	−25.4±4.8	−13.4±8.4
Changes $R_{int_{insp}}$ %	+49.1±29.6	+13.2±11.4
Change $R_{int_{exp}}$ %	+34.3±27.9	+8.8±17.4
Discordance between $R_{int_{insp}}$ and P_{tcO_2} n (%, 95% CI)	11 (55, 34–74)	0 (0, 0–35)
R_{int} increase <35% at $PD_{20}P_{tcO_2}$ n	6	
R_{int} increase ⩾35% before $PD_{20}P_{tcO_2}$ n	5	
Discordance between $PD_{35}R_{int_{insp}}$+$S_{pO_{2,3\%}}$ and P_{tcO_2} n	6	0
Discordance between $R_{int_{exp}}$ and P_{tcO_2} n (%, 95% CI)	16 (80, 58–92)	3 (42, 16–75)
R_{int} increase <35% at $PD_{20}P_{tcO_2}$ n	10	0
R_{int} increase ⩾35% before $PD_{20}P_{tcO_2}$ n	6	3
Discordance between $PD_{35}R_{int_{exp}}$+ $S_{pO_{2,3\%}}$ and P_{tcO_2} 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 P_{tcO_2} ($PD_{20}P_{tcO_2}$) in responsive children and at the last dose of methacholine in nonresponsive children. Discordances between R_{int} and P_{tcO_2} changes were assessed at every steps of the test. R_{int} changes are more or less than 35% increase from the post-diluent value ($PD_{35}R_{int}$). $R_{int_{insp}}$: inspiratory interrupter resistance; $R_{int_{exp}}$: expiratory interrupter resistance; $PD_{35}R_{int_{insp}}$: provocative dose of methacholine causing a 35% decrease in $R_{int_{insp}}$; $S_{pO_{2,3\%}}$: at least 3% decrease in transcutaneous saturation of oxygen from the post-diluent value; $PD_{35}R_{int_{exp}}$: provocative dose of methacholine causing a 35% decrease in $R_{int_{exp}}$.

Our results do not support a universal physiological mechanism to explain discrepancies between Rint and P_{tcO_2} measurements during bronchial challenge in young children. The lack of Rint 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 $R\text{int}_{insp}$ over $R\text{int}_{exp}$ remains unexplained. The early reactivity in Rint (before $PD_{20}P_{tcO_2}$) 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 $R\text{int}_{insp}$ and $R\text{int}_{exp}$ explaining the discrepancies recorded.

To challenge the proposed threshold for Rint [1], we switched from a 35% to a 40% increase and the total number of discordances decreased only for $R\text{int}_{exp}$ although they remained higher than that of $R\text{int}_{insp}$. However, as a Rint device may measure only $R\text{int}_{exp}$, the threshold of 40% may be useful to implement. In children with no Rint increase at $PD_{20}P_{tcO_2}$, 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 Rint and S_{pO_2} measurements when P_{tcO_2} is not available.

In conclusion, $R\text{int}_{insp}$ better detects BHR than $R\text{int}_{exp}$ and might better match $PD_{20}P_{tcO_2}$ changes. Until larger studies confirm these first results, it is reasonable to stick to the proposal of favouring measurement of $R\text{int}_{insp}$ rather than $R\text{int}_{exp}$ 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% $R\text{int}_{insp}$ increase or a 3% S_{pO_2} decrease might be a useful criterion for detecting BHR with respect to P_{tcO_2} changes.

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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 Goaguen, 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.

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