A systematic review of lung function testing in asthmatic young children

Teste funcționale respiratorii realizate la copilul astmatic de vârstă preșcolară

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Abstract

Asthma diagnosis is difficult in young children being mainly based on clinical signs and parents' history, which is sometimes difficult to obtain. Lung function testing may improve asthma diagnosis by objectively assessing its main features, airway obstruction, spontaneously reversible or after use of a bronchodilator drug, ventilation inhomogeneity during an acute bronchoconstriction and airway hyperresponsiveness. In young children that cannot cope with classical tests, it is important to use and develop simple, short lasting methods, made in spontaneous ventilation without active cooperation. Such techniques are a measurement of respiratory resistance by forced oscillations or the interrupter technique, of specific airway resistance by plethysmography and capnography. All these parameters are sensitive to the presence of an airway obstruction and to a bronchodilator or bronchoconstrictor agent, but their cutoff values in differentiating between asthmatic and healthy children as well as their specific indications in asthma management remain to be established.

Keywords: *asthma, child, forced oscillations technique, interrupter technique, specific airway resistance, capnography.*

Rezumat

Diagnosticul astmului bronșic la copilul mic este dificil și se bazează în principal pe semnele și simptomele clinice și pe istoricul bolii descris de către părinți, câteodată greu de obținut. Probele funcționale respiratorii pot ajuta la ameliorarea acestuia prin evaluarea obiectivă a principalelor caracteristici ale astmului: obstrucția bronșica reversibilă spontan sau după administrarea unui medicament bronhodilatator, inomogenitatea ventilației în timpul unei bronhoconstricții acute, hiperreactivitatea bronșică. La copilul mic necooperant cu metodele clasice de explorare funcțională, este important să folosim metode simple, de scurtă durată, realizate în ventilație spontană, fără anestezie, care să nu necesite cooperarea activă. Astfel de metode sunt reprezentate de măsurarea rezistenței respiratorii prin tehnica de oscilații forțate sau de întrerupere a debitului de aer, a rezistenței specifice a căilor aeriene prin pletismografie și capnografia. Parametrii obținuți prin aceste tehnici sunt sensibili la prezența unei obstrucții bronșice și la un agent bronho- constrictor sau dilatator, dar valorile lor prag pentru a diferenția copiii astmatici de cei sănătoși ca și indicațiile lor specifice în managementul astmului rămân a fi stabilite.

Cuvinte-cheie: *astm bronșic, copil, tehnica de oscilații forțate, tehnica de întrerupere a debitului de aer, rezistența specifică a căilor aeriene, capnografia*

General data

Asthma is the leading cause in young child morbidity due to a chronic condition, as measured by school and professional absenteeism and hospitalizations[1]. It is the most common chronic disease in children, with a high prevalence, especially in preschoolers, from 10.8%[2] reaching up to 20%[3]. This may be explained by diagnosis, treatment and evaluation difficulties at this age. Asthma diagnosis is based on the clinical signs and symptoms and medical history described by parents, which is not easily obtained. Lung function testing may confirm the diagnosis by an objective assessment of asthma's main physiopathological features: chronic inflammation of the bronchial mucosa, bronchial obstruction spontaneously reversible or after a bronchodilator administration, ventilation inhomogeneity during an acute bronchoconstriction and bronchial hyperresponsiveness.

The standard technique for defining a bronchial obstruction at baseline, an excessive response to a beta2mimetic agent inhalation and a bronchial hyperresponsiveness is spirometry. A forced expiratory maneuver requires patient's full cooperation, its complete understanding to perform it in a reproducible manner, and can be difficult to achieve in small children. Furthermore, the threshold defining a positive bronchodilator response in children is not known. Current recommendations for adults are an increase of 12% and 200 ml in FEV_1 (forced expiratory volume in the first second) relative to its baseline[4]. These recommendations cannot be applied in children because of their much lower lung volumes. Two studies[5,6] showed that a threshold of 10% is significant with a sensitivity of 0.91 and specificity of 0.95. In young children, Aurora et al.[7] suggested the use of $FEV_{0.5}$ (forced expiratory volume in 0.5 seconds) or $FEV_{0.75}$ (forced expiratory volume in 0.75 seconds) due to their shorter forced expiration time, these parameters reflecting more accurately the bronchial caliber. $FEV_{0.5}$ may also be used in school-aged children usually presenting a FEV_1 reported to FVC (forced vital capacity) higher than in adults. Moreover, the bronchomotor tone significantly influences the spirometry results even in non asthmatic non atopic children[8-10]. Simpler, short-lasting lung function testing methods are needed in preschoolers, performed in tidal breathing without anesthesia. Such methods are the measurement of respiratory resistance (Rrs) by the forced oscillation technique or flow interruption (Rint) or specific airway resistance (sRaw) by plethysmography. Rrs, Rint and sRaw may be used to demonstrate a positive response to a bronchodilator or a bronchoconstrictor agent. FEV_1 is dependent on airway caliber and their wall compliance[11]. It was shown as an alteration in FEV_1 after Salbutamol inhalation in children with cystic fibrosis due to the increase in airway compliance during forced expiration[11]. In contrast, Rrs improved after Salbutamol because the forced oscillation technique is performed during spontaneous breathing without the need of a forced expiratory maneuver. Therefore, Rrs is less dependent on bronchial wall elastic properties. But significant Rrs, Rint and sRaw responses to Salbutamol were identified also in healthy children[8,9,11], so that reversibility thresholds are not well defined.

In preschool children, Rrs, Rint or sRaw significantly increased compared to their baseline values after a bronchial challenge test[12-16]. The sensitivity of these methods was low and there were discrepancies between the resistance and other functional parameters change[17].

Another non-invasive technique, performed in tidal breathing in an uncooperative child is capnography. It consists of measuring the CO_2 concentration in the expired air, mainly used to assess ventilation inhomogeneity during an acute airway obstruction. Capnogram shape is sensitive to an airway obstruction and to a bronchodilator treatment.

In consequence, lung function testing in preschool children is now feasible[17]. Recent progress allowed the development of appropriate methods for pediatric age. These techniques still need standardization to be routinely used in young children and to provide specific indications for each test for the asthmatic child management. These methods require child passive cooperation and their contribution to asthma diagnosis will be presented in the following paragraphs.

Forced oscillation technique

Described for the first time by DuBois in 1956[18], this method consists of applying pressure oscillations superposed on the subject's spontaneous breathing that will induce mechanical changes in the respiratory system. These pressure variations are obtained using a sinusoidal excitation signal generated with a loudspeaker at a frequency higher than the patient's respiratory rate, ranging usually between 4 and 48 Hz, and resulting airflow is measured. The oscillations are applied directly to the subject's mouth, a technique called "standard generator". The child is seated, wearing a nose clip and breathing through a mouthpiece equipped with an antibacterial filter, connected to a pneumotachograph. The measurement starts after a short period of time when ventilation is monitored to ensure the patient breathes calmly and regularly, and lasts 30-45 seconds. The measurements are visualized and those not meeting quality criteria (presence of swallowing, glottis closure, improper nose sealing, irregular breathing, hyperventilation[19]) are removed. The respiratory impedance (Zrs) is obtained by this technique, a complex parameter, the pressure to flow ratio[19]. Zrs is composed of a real part, respiratory resistance (Rrs), and an imaginary part, respiratory reactance (Xrs). Rrs describes the respiratory system resistive properties and reflects the bronchial caliber, being a more specific parameter than FEV_1[20]. Xrs reflects, at low frequency, the lung elastic properties, the elastance, the inverse of compliance, and at high frequencies, its inertial properties, the inertance[21].

Several studies reported a good reproducibility of the "standard generator" method in young children over 3 years of age. Rrs at 8 Hz significantly increased during[22] or 2-3 days after an asthma crisis[23], being correlated to clinical indices of airways dysfunction severity. Xrs was significantly negative in these patients compared to controls[23]. These differences were not observed in well-controlled, stable asthmatic patients, at baseline[24].

Zrs obtained by the "standard" method is underestimated[25] because a part of input flow is lost due to upper airways wall vibration, inducing an artifact. This shunt is even more important in younger children and in the presence of a bronchial obstruction[26].

The artifact may be minimized by applying the pressure oscillations around the subject's head that is surrounded by a plexiglass box[27], the "head-generator" method. This apparatus is available only in a few specialized lung function testing labs and sometimes accepted with difficultly by little children.

Another option to remove the artifact, especially when studying a bronchodilator or bronchoconstrictor agent effect, is using a parameter called respiratory admittance (Ars). Ars is the inverse of Zrs (1/Zrs) and when computing it, upper airways admittance is in parallel with respiratory admittance and its change induced by a bronchomotor agent is independent of the upper airway artifact. Ars was first described by Farré in 1999[28] in a study that included asthmatic children aged 2 to 9 years performing a bronchial challenge by acetylcholine or allergen inhalation. Ars variation, expressed as the difference between the Ars post- and pre- bronchial challenge, was not different between "standard generator" and "head generator" methods, being significantly correlated, while Rrs variation was underestimated by "standard generator" method[28].

A study conducted by Nguyen et al. on asthmatic children showed that Rrs significantly improved after salbutamol inhalation compared to its baseline value by both methods, and the Ars bronchodilator response was similar by the two methods, while that of Rrs was underestimated by the "standard generator" method[29]. Mazurek et al. showed that the "head generator" method improved Rrs specificity compared to the "standard generator" method (78% vs 65%) in children with asthma and cystic fibrosis[30].

For Rrs, it is recommended as a positive bronchodilator response a decrease of 19%[22] or of 40% reported to its baseline value[11,24], depending if measurements are performed during an asthma crisis or not, while for Xrs, an increase of 65%[24] is needed.

In preschoolers, a positive bronchoconstrictor response to a challenge was considered an increase of 40-50% in Rrs, this threshold being correlated to an increase of 20% in FEV_1[31].

Specific airway resistance by plethysmography

Described for the first time by DuBois in 1956[32], total body plethysmography allows for the thoracic gas volume to be obtained using Boyle-Mariotte's law and airway resistance, the ratio between specific airway resistance and thoracic gas volume. The measurement requires patient's full cooperation to perform intrapulmonary gas compression and distension maneuvers (panting) while the airways are occluded by a shutter, and is difficult before 5-6 years of age. For younger children, sRaw may be obtained by a single step performed in tidal breathing, by measuring airflow and volume changes during inspiration and expiration, without any special respiratory maneuver or shutter closing[33-36].

This method has been successfully applied to children over 2 years of age[34,37,38]. The success rate in young children can be improved if one parent accompanied him into the plethysmograph box[35]. Airway resistance varies inversely proportional to lung volume[36] so that, sRaw, the product between airway resistance and thoracic gas volume, would be a more stable parameter able to differentiate between the effect of diseases and physiological effect of growth and development[33]. After 8 years of age, sRaw values are independent of age, height or gender and only minimally influenced by respiratory rate[38].

There are several parameters that can be reported by sRaw measurement, the recommendations are to use effective resistance, computed by a method integrating multiple points throughout the breathing cycle, and not the total resistance measured between the maximum plethysmograph pressure points[33]. Effective resistance reflects more accurately airway mechanics[39,40] and includes resistive changes along the breathing cycle compared to the total resistance. Their difference is very small in healthy subjects, but increases in obstructive pathologies.

Air cooling and condensation during expiration, its heating and humidification during inspiration, induce a thermal artifact that influences the relationship between volume changes measured by plethysmograph and airflow. This artifact can be minimized by a digital correction available on all commercial plethysmographs or by making rapid respiratory efforts (panting), sRaw being overestimated by digital correction compared to the panting method[41].

sRaw reflects the overall airway caliber, including lung expansion effect[42].

sRaw is a parameter sensitive to a bronchial obstruction, detecting a positive response to a bronchodilator agent with an excellent reproducibility[38].

The presence of at least one episode of wheezing or atopy or atopic parents will result in an abnormal lung function at 3 years of age, even in the absence of respiratory symptoms, reflected by sRaw high values, measured in tidal breathing[43].

A decrease of 25% in sRaw after salbutamol inhalation reported to its predictive value is recommended as the threshold to differentiate asthmatic and healthy children aged 2 to 5 years, with a sensitivity of 66% and a specificity of 81%[8]. In older children, aged 6 to 18 years, Mahut et al. showed that a 42% decrease in sRaw after bronchodilator presented a good specificity in predicting a 12% decrease in FEV_1, this threshold not being influenced by the subject's height or age[44].

In asthmatic preschoolers, a positive bronchoconstrictor response was considered an increase of 100% in sRaw during a bronchial challenge related to its baseline[13,15], higher than the threshold of 45% recommended in adults[45]. Other studies showed that an increase of 38% in sRaw reported to its baseline was more sensitive in detecting a bronchoconstrictor response than FEV_1[13].

Resistance by flow interrupter technique

This technique was first described in 1927 by Von Neergaard[46] and consists of rapid and complete airway occlusions during a normal breathing cycle while flow and pressure are recorded at the mouth[47-49]. The principle is that during a sudden interruption of the airflow, the mouth and alveolar pressure will quickly equilibrate, Rint being defined as the ratio of the equilibrium pressure to airflow measured immediately before the interruption.

The child, accompanied by his parents[38], is seated, wearing a nose clip, his neck slightly extended. His cheeks are supported by a technician in order to decrease the upper airway compliance. He breathes calmly through a mouthpiece equipped with an antibacterial filter, connected to a pneumotachograph[17]. The airflow is interrupted during expiration being triggered by a predetermined flow (or volume) that coincides to the peak expiratory flow and lasting 100 ms. 10 occlusions are recorded and at least five acceptable maneuvers are retained, their median being reported. Pressure-time curves are examined at the end of the test and those showing air leaking around the mouthpiece, neck in hyperextension or flexion during measurement, vocalization or movement of the tongue during respiration or abnormal breathing pattern, are eliminated[17].

When the mouth airflow is suddenly interrupted, a rapid, initial change in mouth pressure will take place, reflecting the pressure difference due to airway resistance at the interruption moment[50] and to lung and thoracic wall resistances[47]. This is followed by a slower change of pressure due to airways tissue viscoelastic properties up to a plateau, representing the elastic recoil of the respiratory system[51].

Measurements may be performed in inspiration or expiration. It is recommended to use expiratory Rint due to higher sensitivity in detecting an induced airway obstruction[38], a better signal-to-noise ratio with higher airflows and a passive mechanical system in expiration[17].

Rint can be easily and repeatedly measured in children over 3 years of age, Rint being correlated with spirometry, oxygen transcutaneous pressure in asthmatic and healthy children but also with sRaw[38].

Airway resistance is accurately estimated by this technique if a mild to moderate bronchial obstruction is present[49]. In case of severe airway obstruction or ventilation inhomogeneity, the necessary time for mouth and alveolar pressure equilibration increases, Rint being underestimated[50].

In children aged 3 to 8 years, a decrease of 35% in Rint after bronchodilator inhalation was considered the optimal threshold to separate healthy and asthmatic children with a specificity of 92% and a sensitivity of 24%[52]. A pre-bronchodilator to post-bronchodilator Rint ratio of more than 1.22 has shown to differentiate between healthy children and those with a history of wheezing aged 2 to 5 years[53].

An increase of 35% in Rint reported at baseline discriminated between responders and non responsive children with chronic cough aged 4 to 6 years[54]. Another study, including children aged 6 to 13 years showed that Rint significantly increased with increasing methacholine doses, but with a low sensitivity and specificity in detecting a bronchial hyperresponsiveness[55].

Capnography

Capnography is a technique that measures the CO_2 concentration in expired air. It is a simple, noninvasive method, performed in tidal breathing. It requires neither patient's sedation nor his active cooperation. The child is seated in a chair or lying on the bed, the device being connected to his nostrils via a nasal cannula, ensuring he breathes through the nose with the mouth closed. Capnogram shape, the CO_2 concentration versus time plot, is sensitive to a bronchial obstruction. Its assessment at baseline and after a bronchodilator administration enhances asthma diagnosis.

In healthy subjects, trhe capnogram has an almost rectangular shape[56] with 4 main phases[57-59]: expiration of anatomic dead space gas, the baseline (phase I); the ascending, almost vertical phase, transition from dead space gas to alveolar gas (phase II); the alveolar plateau, alveolar gas expiration (phase III); the descending, almost vertical phase, onset of a new inspiration (phase IV). Capnogram shape may be characterized by indices analyzing all its phases, allowing the indirect measurement of bronchoconstriction if present. These shape indices, described in previous studies[56,57,60,61], are: phase II slope; phase III slope; angle between phase II and III; the first peak of the capnogram first-order derivative, reflecting phase II; and the first trough of the capnogram second-order derivative, reflecting the curvature between phase II and III[59].

The capnogram rectangular shape changes in the presence of an airway obstruction due to ventilation inhomogeneity[57] with altered ventilation to perfusion ratio. A bronchospasm changes the ventilation pattern and the alveoli will not evenly fill with air during inspiration. During expiration, they will empty asynchronously leading to a progressive increase in CO_2 concentration in expired gas. Consequently, the ascending phase and the alveolar plateau will change their shape, becoming a "shark fin", a characteristic pattern of asthma[57], with a flatter phase II slope, steeper phase III slope, an opening of the angle between the 2 phases[59]. Capnogram shape indices are sensitive to bronchial obstruction and to bronchodilator therapy.

These indices correlated significantly with spirometric parameters in asthmatic adults, particularly those related to alveolar plateau[57], phase III slope being steeper than in healthy subjects[62]. In patients aged 10 to 71 years presenting an asthma attack, the capnogram shape changed after bronchodilator treatment with a significant difference in phase III slope and angle between phase II and III but not for phase II slope[56]. Stromberg et al. demonstrated that in children, an induced bronchial obstruction is usually associated with a pathological capnogram[63].

Children with persistent, controlled asthma presented an increase in spirometric parameters, a decrease in phase II slope normalized to tidal volume, without phase III slope change, after bronchodilator treatment[60]. In an experimental study including intubated, artificially ventilated rabbits, phase II slope, the first peak of the capnogram first-order derivative and the first trough of the capnogram second-order derivative were significantly altered in response to an acute airway obstruction reported to baseline even at high breathing rates. The phase III slope and the angle between phase II and III were significantly correlated with forced oscillation technique parameters. The study concluded that capnography may be used to identify an acute bronchoconstriction even at high breathing rates[59] usually presented by young children during an asthma crisis. Capnography is a feasible and reproducible technique in asthmatic children[61].

Conclusion

Lung function testing methods presented in this paper are performed in tidal breathing. They can be successfully applied in awake preschool children, without anesthesia. The measurements obtained are satisfactory from a technical point of view, being more suitable for children not able to perform a reproducible spirometry.

When comparing these methods, sRaw and Xrs were the most sensitive parameters in detecting a bronchoconstriction, followed by FEV_1 and Rrs or Rint [12,13,64]. sRaw and Rrs responses to bronchodilator appear to be very useful in identifying asthmatic children while capnography and Xrs have a common interest in detecting an acute bronchoconstriction. But the role of these different techniques and different parameter thresholds to define a clinically significant bronchodilator / bronchoconstrictor response remains to be established. ■

References

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy.* 2004;59(5):469-78.
2. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet.* 1998;351(9111):1225-32.
3. Haby MM, Peat JK, Marks GB, Woolcock AJ, Leeder SR. Asthma in preschool children: prevalence and risk factors. *Thorax.* 2001;56(8):589-95.
4. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *The European Respiratory Journal.* 2005;26(5):948-68.
5. Delacourt C, Lorino H, Herve-Guillot M, Reinert P, Harf A, Housset B. Use of the forced oscillation technique to assess airway obstruction and reversibility in children. *Am J Respir Crit Care Med.* 2000;161(3 Pt 1):730-6.
6. Zerah F, Lorino AM, Lorino H, Harf A, Macquin-Mavier I. Forced oscillation technique vs spirometry to assess bronchodilatation in patients with asthma and COPD. *Chest.* 1995;108(1):41-7.
7. Aurora P, Stocks J, Oliver C, Saunders C, Castle R, Chaziparasidis G, et al. Quality control for spirometry in preschool children with and without lung disease. *Am J Respir Crit Care Med.* 2004;169(10):1152-9.
8. Nielsen KG, Bisgaard H. Discriminative capacity of bronchodilator response

References

measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. *Am J Respir Crit Care Med.* 2001;164(4):554-9.
9. Beydon N, Amsallem F, Bellet M, Boule M, Chaussain M, Denjean A, et al. Pre/postbronchodilator interrupter resistance values in healthy young children. *Am J Respir Crit Care Med.* 2002;165(10):1388-94.
10. Pichon A, Roulaud M, Denjean A, de Bisschop C. Airway tone during exercise in healthy subjects: effects of salbutamol and ipratropium bromide. *Int J Sports Med.* 2005;26(5):321-6.
11. Hellinckx J, De Boeck K, Bande-Knops J, van der Poel M, Demedts M. Bronchodilator response in 3-6.5 years old healthy and stable asthmatic children. *The European respiratory journal.* 1998;12(2):438-43.
12. Klug B, Bisgaard H. Assessment of bronchial hyperresponsiveness in preschool children: methodological issues. *Pediatr Allergy Immunol.* 1996;7(9 Suppl):25-7.
13. Bisgaard H, Klug B. Lung function measurement in awake young children. *The European respiratory journal.* 1995;8(12):2067-75.
14. Beydon N, Trang-Pham H, Bernard A, Gaultier C. Measurements of resistance by the interrupter technique and of transcutaneous partial pressure of oxygen in young children during methacholine challenge. *Pediatric pulmonology.* 2001;31(3):238-46.
15. Badier M, Guillot C, Dubus JC. Bronchial challenge with carbachol in 3-6-year-old children: body plethysmography assessments. *Pediatric pulmonology.* 1999;27(2):117-23.
16. Wilson NM, Bridge P, Silverman M. Bronchial responsiveness and symptoms in 5-6 year old children: a comparison of a direct and indirect challenge. *Thorax.* 1995;50(4):339-45.
17. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, 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(12):1304-45.
18. Dubois AB, Brody AW, Lewis DH, Burgess BF, Jr. Oscillation mechanics of lungs and chest in man. *J Appl Physiol.* 1956;8(6):587-94.
19. Oostveen E, MacLeod D, Lorino H, Farre R, Hantos Z, Desager K, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *The European respiratory journal.* 2003;22(6):1026-41.
20. Navajas D, Farre R. Forced oscillation assessment of respiratory mechanics in ventilated patients. *Crit Care.* 2001;5(1):3-9.
21. Marchal F, Loos N, Schweitzer C, Gauthier R. Several aspects of respiratory function testing in children. *Rev Mal Respir.* 2000;17(1):67-75.
22. Ducharme FM, Davis GM. Respiratory resistance in the emergency department: a reproducible and responsive measure of asthma severity. *Chest.* 1998;113(6):1566-72.
23. Vu LT, Demoulin B, Nguyen MT, Nguyen YT, Marchal F. Respiratory impedance and response to salbutamol in asthmatic Vietnamese children. *Pediatric pulmonology.* 2010;45(4):380-6.
24. Thamrin C, Gangell CL, Udomittipong K, Kusel MM, Patterson H, Fukushima T, et al. Assessment of bronchodilator responsiveness in preschool children using forced oscillations. *Thorax.* 2007;62(9):814-9.
25. Peslin R, Duvivier C, Gallina C, Cervantes P. Upper airway artifact in respiratory impedance measurements. *The American review of respiratory disease.* 1985;132(3):712-4.
26. Marchal F, Haouzi P, Peslin R, Duvivier C, Gallina C. Mechanical properties of the upper airway wall in children and their influence on respiratory impedance measurements. *Pediatric pulmonology.* 1992;13(1):28-33.
27. Marchal F, Mazurek H, Habib M, Duvivier C, Derelle J, Peslin R. Input respiratory impedance to estimate airway hyperreactivity in children: standard method versus head generator. *The European respiratory journal.* 1994;7(3):601-7.
28. Farre R, Rotger M, Marchal F, Peslin R, Navajas D. Assessment of bronchial reactivity by forced oscillation admittance avoids the upper airway artefact. *The European respiratory journal.* 1999;13(4):761-6.
29. Nguyen YT, Demoulin B, Schweitzer C, Bonabel-Chone C, Marchal F. Identification of bronchodilator responsiveness by forced oscillation admittance in children. *Pediatric research.* 2007;62(3):348-52.
30. Mazurek HK, Marchal F, Derelle J, Hatahet R, Moneret-Vautrin D, Monin P. Specificity and sensitivity of respiratory impedance in assessing reversibility of airway obstruction in children. *Chest.* 1995;107(4):996-1002.
31. Duiverman EJ, Neijens HJ, Van der Snee-van Smaalen M, Kerrebijn KF. Comparison of forced oscillometry and forced expirations for measuring dose-related responses to inhaled methacholine in asthmatic children. *Bull Eur Physiopathol Respir.* 1986;22(5):433-6.
32. Dubois AB, Botelho SY, Comroe JH, Jr. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. *J Clin Invest.* 1956;35(3):327-35.
33. Kirkby J, Stanojevic S, Welsh L, Lum S, Badier M, Beardsmore C, et al. Reference equations for specific airway resistance in children: the Asthma UK initiative. *The European respiratory journal.* 2010;36(3):622-9.
34. Bisgaard H, Nielsen KG. Plethysmographic measurements of specific airway resistance in young children. *Chest.* 2005;128(1):355-62.
35. Klug B, Bisgaard H. Measurement of the specific airway resistance by plethysmography in young children accompanied by an adult. *The European respiratory journal.* 1997;10(7):1599-605.
36. Dab I, Alexander F. A simplified approach to the measurement of specific airway resistance. *Pediatric research.* 1976;10(12):998-9.
37. Nielsen KG, Bisgaard H. Hyperventilation with cold versus dry air in 2- to 5-year-old children with asthma. *Am J Respir Crit Care Med.* 2005;171(3):238-41.
38. Courriel JM, Child F. Applied physiology: lung function testing in children. *Current Paediatrics.* 2004;14:444-51.
39. Jaeger MJ, Otis AB. Measurement of airway resistance with a volume displacement body plethysmograph. *J Appl Physiol.* 1964;19:813-20.
40. Manzke H, Stadlober E, Schellauf HP. Combined body plethysmographic, spirometric and flow volume reference values for male and female children aged 6 to 16 years obtained from "hospital normals". *Eur J Pediatr.* 2001;160(5):300-6.
41. Coutier L, Varechova S, Demoulin B, Bonabel C, Roman-Amat C, Tuan TL, et al. Specific airway resistance in children: panting or tidal breathing? *Pediatric pulmonology.* 2014;49(3):245-51.
42. Nielsen KG. Plethysmographic specific airway resistance. *Paediatric respiratory reviews.* 2006;7 Suppl 1:S17-9.
43. Lowe L, Murray CS, Custovic A, Simpson BM, Kissen PM, Woodcock A. Specific airway resistance in 3-year-old children: a prospective cohort study. *Lancet.* 2002;359(9321):1904-8.
44. Mahut B, Peiffer C, Bokov P, Delclaux C, Beydon N. Use of specific airway resistance to assess bronchodilator response in children. *Respirology.* 2011;16(4):666-71.
45. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med.* 2000;161(1):309-29.
46. Von Neergaard J, Wirz K. Die Messung der Stro¨ mungswidersta¨nde in den Atemwegen des Menschen, insbesondere bei Asthma und Empfysem. *Z Klin Med.* 1927(105):51-82.
47. Mead J, Whittenberger JL. Evaluation of airway interruption technique as a method for measuring pulmonary airflow resistance. *J Appl Physiol.* 1954;6(7):408-16.
48. Bates JH, Baconnier P, Milic-Emili J. A theoretical analysis of interrupter technique for measuring respiratory mechanics. *Journal of applied physiology.* 1988;64(5):2204-14.
49. Jackson AC, Milhorn HT, Jr., Norman JR. A reevaluation of the interrupter technique for airway resistance measurement. *J Appl Physiol.* 1974;36(2):264-8.
50. Bates JH, Rossi A, Milic-Emili J. Analysis of the behavior of the respiratory system with constant inspiratory flow. *Journal of applied physiology.* 1985;58(6):1840-8.
51. Sly PD, Bates JH. Computer analysis of physical factors affecting the use of the interrupter technique in infants. *Pediatric pulmonology.* 1988;4(4):219-24.
52. Beydon N, Pin I, Matran R, Chaussain M, Boule M, Alain B, et al. Pulmonary function tests in preschool children with asthma. *Am J Respir Crit Care Med.* 2003;168(6):640-4.
53. McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. *The European respiratory journal.* 2000;15(5):833-8.
54. Beydon N, Matran R, Wuyam B, Amsallem F, Boule M, Alberti C, et al. Methacholine challenge in young children: measurement of resistance by interruption. *Rev Mal Respir.* 2005;22(6 Pt 1):959-66.
55. Koopman M, Brackel HJ, Vaessen-Verberne AA, Hop WC, van der Ent CK. Evaluation of interrupter resistance in methacholine challenge testing in children. *Pediatric pulmonology.* 2011;46(3):266-71.
56. Howe TA, Jaalam K, Ahmad R, Sheng CK, Nik Ab Rahman NH. The use of end-tidal capnography to monitor non-intubated patients presenting with acute exacerbation of asthma in the emergency department. J Emerg Med. 2011;41(6):581-9.
57. You B, Peslin R, Duvivier C, Vu VD, Grilliat JP. Expiratory capnography in asthma: evaluation of various shape indices. *The European respiratory journal.* 1994;7(2):318-23.
58. Kodali BS. http://www.capnography.com: an animated website. *Anesth Analg.* 2001;93(5):1364.
59. Ioan I, Demoulin B, Duvivier C, Leblanc AL, Bonabel C, Marchal F, et al. Frequency dependence of capnography in anesthetized rabbits. *Respiratory physiology & neurobiology.* 2014;190:14-9.
60. Almeida CC, Almeida-Junior AA, Ribeiro MA, Nolasco-Silva MT, Ribeiro JD. Volumetric capnography to detect ventilation inhomogeneity in children and adolescents with controlled persistent asthma. *J Pediatr (Rio J).* 2011;87(2):163-8.
61. Evered L, Ducharme F, Davis GM, Pusic M. Can we assess asthma severity using expiratory capnography in a pediatric emergency department? *CJEM.* 2003;5(3):169-70.
62. Yaron M, Padyk P, Hutsinpiller M, Cairns CB. Utility of the expiratory capnogram in the assessment of bronchospasm. *Ann Emerg Med.* 1996;28(4):403-7.
63. Stromberg NO, Gustafsson PM. Ventilation inhomogeneity assessed by nitrogen washout and ventilation-perfusion mismatch by capnography in stable and induced airway obstruction. *Pediatric pulmonology.* 2000;29(2):94-102.
64. Phagoo SB, Wilson NM, Silverman M. Evaluation of the interrupter technique for measuring change in airway resistance in 5-year-old asthmatic children. *Pediatric pulmonology.* 1995;20(6):387-95.