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Lung function tests to monitor respiratory disease in preschool children

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Summary. Pulmonary function tests are routinely used in the diagnosis and follow-up of respiratory diseases. In preschool children assessment and evaluation of lung function has always been challenging but improved techniques that require only minimal collaboration allowed obtaining reliable and useful results even in this group of patients. In this review we will describe the different techniques used in clinical practice to measure lung function in preschool children. (www.actabiomedica.it)

Key words: preschool, lung function, interrupter, forced oscillations, airway resistance, multiple breath washout

Introduction

Pulmonary function testing plays a key role in the diagnosis and follow-up of respiratory disease (1, 2). However, performing the tests and obtaining objective results in preschool children (i.e. 2-5 years) has always been very challenging due to the poor cooperation in this age range. Ongoing research in this field has allowed to improve the techniques and obtain reliable and useful results even in this group of patients.

In infants lung volumes can be measured by plethysmography (that can measure also airway resistance) or multiple-breath inert gas washout (MBW) with the infant sleeping in a supine position with or without sedation. Other tests are also used to assess forced expiratory flow-volume loops and respiratory mechanics in sedated infants. However, all these techniques are difficult to use in routine clinical practice and are performed in a few specialised centres.

For older children (>2-3 years), who can provide a minimal collaboration, lung volumes and forced expiratory flows can be assessed by means of spirometry using specific criteria of acceptability. Plethysmography, interrupter technique (Rint) and forced oscillation technique (FOT) can be performed to measure respiratory resistance and reactance. Published international guidelines and reference values can now facilitate the clinical use of some of these tests.

This review aims to describe the different techniques that can be used in clinical practice to measure lung function in preschool children. Plethysmography in this age is less standardised and problematic to use routinely and it will not be included in this review.

Interrupter technique

The interrupter technique measures respiratory resistance (Rint) (including lung, airways and rib cage) during tidal breathing. Therefore, it is a quick and non-invasive test that can be used in preschoolers not enough collaborative to perform spirometry. The child will be sitting, wearing a nose clip, with the head in a neutral position and the cheeks supported by the hands of an operator. During tidal breathing through a mouthpiece and bacterial filter, a valve closing in less than 10 ms will interrupts the flow in correspondence of the peak expiratory flow for about 100 ms. In this fashion the pressure at the mouth quickly equilibrates with pressure in the alveoli, giving an estimate of the pressure in the airways. Respiratory resistance is then calculated as the ratio between the change in mouth pressure and the flow measured immediately before ("classical" technique) or after ("opening" technique) the interruption.

Because of the viscoelastic properties of the respiratory system, when pressure is measured at the beginning of the interruption Rint will tend to measure pure airway resistance, when pressure is measured at the end of the interruption Rint will approach the resistance of the whole respiratory system including lung tissue and rib cage. Several methods of measuring mouth pressure have been proposed: in the "classical" technique, mouth pressure is back-extrapolated to 0 ms from 30 and 70 ms after the interruption (Fig. 1); in the "opening" technique, mouth pressure is measured at the end of the interruption. Usually, ten measurements are recorded to obtain at least five acceptable measurements of which the median is reported (3).

In preschool children the interrupter technique is highly feasible with up to 98% of subjects able to perform the test (4). Reference equations for the Italian population for the classic technique have been published (4) and international reference values are also available (5).

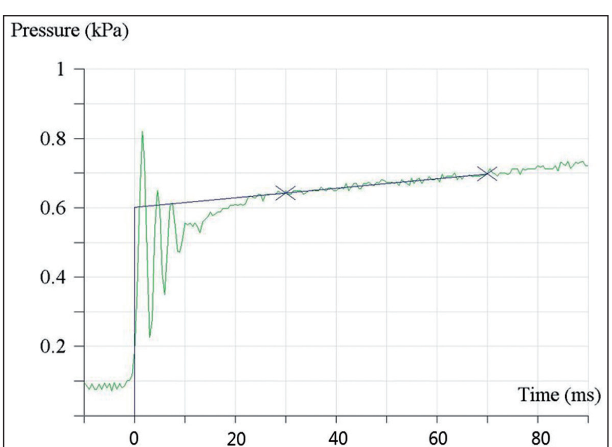

Figure 1. Rint, classical technique: mouth pressure is back-extrapolated to 0 ms from 30 and 70 ms after the interruption

Several reports have been published on Rint in preschool children with wheezing. When used to compare children with different wheezing phenotypes, Rint was found to be higher in children with persistent wheeze compared to never wheezers and children with transient symptoms (6, 7). However, Rint measurements in young children failed to predict the development of asthma at school age (8, 9). As for spirometry, also for Rint assessing bronchodilator response (BDR) can be very useful in daily clinical practice. In one of the studies on BDR in preschool children, a decrease in Rint ≥0.26 $kPa \cdot L^{-1} \cdot s$ (≥1.25 if expressed in Z-scores) after bronchodilation could discriminate children with respiratory symptoms at the time of the test with a sensitivity of 80% and a specificity of 82% (10). Hence, this cut-off could be appropriate for assessing BDR in preschool wheezing children. Other data from the literature show that BDR measured with Rint can distinguish children with wheeze from healthy children with a sensitivity that varies from 24% to 76% and a specificity between 70% and 92% (11).

In preschool children with cystic fibrosis (CF) Rint was assessed in a few studies. In a case-control study involving children aged 3-5 years Rint distinguished patients with asthma or CF from healthy controls showing higher resistance in the case population, but these values did not differ between the two diseases (12). Greater Rint values in preschool children with CF were also reported by Beydon et al. who demonstrated the highest resistance in the subjects exposed to passive smoke (13). When used in longitudinal studies, Rint could not reflect the progression of the disease and the worsening seen at the chest X rays did not correlate with changes of airway resistance over a 3 year period (14).

Only two studies used Rint in preschool children born preterm and compared lung function in children with and without bronchopulmonary dysplasia (BPD) (15, 16). Children diagnosed with BPD had stiffer airways as demonstrated by higher values of resistance (15, 16). In addition, prematurity alone was associated with higher airway resistance compared to reference values (16).

In summary, Rint can be a feasible and useful technique to assess airway resistance in preschool children with asthma, CF and BPD.

Forced oscillation technique

Similarly to Rint, the forced oscillation technique (FOT) is a non-invasive technique performed during tidal breathing that requires only minimal cooperation from the patient. Small pressure oscillations at frequencies between 4 and 48 Hz are applied to the airways and the impedance of the respiratory system (Zrs) is calculated from the resulting changes of mouth pressure and flow (3). Zrs comprises respiratory resistance (Rrs) and respiratory reactance (Xrs) (17). Rrs includes airway, lung tissue and chest wall resistance and represents the frictional pressure loss in the airway, while Xrs represents the balance of respiratory elastance (1/compliance) and inertance. Elastic forces give a negative Xrs and are predominant at low frequencies, while inertial forces give a positive Xrs and are predominant at high frequencies; the frequency at which elastic and inertial forces equal each other (resulting in 0 Xrs) is called resonant frequency (Fres). AX is the total reactance (area under the curve) at all frequencies between 4-5 Hz and Fres and reflects Xrs at low frequencies and thus the elastance of the respiratory system.

The pressure oscillation applied to the mouth (forcing signal) can be a sinusoidal wave or a series of impulses (IOS), and both can be used at a single frequency or as multiple-frequency composite signals. Since low frequencies (4-10 Hz) can reach the peripheral lung while high frequencies (18-22 Hz) can be transmitted only into the central airways (18), the lowest frequencies represent an estimate of the whole respiratory system and the highest frequencies an estimate of the upper airways. The difference between Rrs at 5 Hz and Rrs at 20 Hz (R5-20) has been used to express the resistance of the peripheral airways (19). However, due to shunt and serial heterogeneity (20), the difference between Rrs at low and high frequencies can be an estimate of the resistance of any level of the airways. Also, the analysis can be performed in the frequency domain (spectral analysis), giving the mean Zrs over the whole recorded breathing period, or in the time domain (within-breath analysis), giving the mean inspiratory and expiratory Zrs for each breath (20) or even the end-inspiratory and end-expiratory Zrs for each breath (21).

To obtain a valid manoeuvre the subject has to breath tidally into a mouthpiece and anti-bacterial filter for at least 8-16 seconds, wearing a nose clip and with the cheeks supported by the hands of an operator (3) (Fig. 2). At least 3 reproducible manoeuvres without artefacts due to coughing, swallowing, vocalization or breath holding have to be obtained to consider valid the test. The mean value of each index are then calculated (3, 11).

A certain number of clinical studies have established reference values for FOT in young children and, as for spirometry, the standing height appears to be the best and only independent variable for the regression equations (3, 11, 22-31).

Many studies have measured lung function with FOT in young wheezy children with conflicting results: some studies reported abnormal lung function (32, 33), while others showed no difference from controls (34, 35). However, a novel method using the within-breath analysis detected airway obstruction with a sensitivity of 92% and a specificity of 89% (21). Cut-offs for BDR have also been suggested: -32% for Rrs8, +65% for Xrs8 and -82% for AX (30). In young children with intermittent asthma IOS predicted the probability of acute exacerbations better than FEV_1 and methacholine challenge (36), with R5 showing a sensitivity of 68% and a specificity of 83% and R5-20 a sensitivity of 90% and a specificity of 57%. Impaired R10 in children with asthma was reported in a cohort of 3-6 year-old Asian children (37) and lower z-scores of reactance Xrs5 distinguished between intermittent and persistent asthma in 162 subjects aged 2-5 years

Figure 2. Forced oscillation technique in a preschool child (permission obtained by parents to reproduce this picture)

(38). In 157 asthmatic children R5 negatively correlated with pre and post-bronchodilator FEV_1, FEV_1/FVC and MEF50 and in a multivariate analysis increased Rrs5 was associated with decreased post-bronchodilator FEV_1 and FEV_1/FVC with a specificity of 85% and 86% respectively (39). BDR could add important information in preschool children who wheezed and could distinguish asthmatic children from controls (35, 37, 40, 41). These findings suggest that wheezing can be associated with airways with higher resistance and lower reactance even in early age. It can be speculated that these impairments may persist in the subjects at risk of persistent asthma.

Although with a pulmonary function within the normal range, preschool children with CF showed higher Rrs and lower Xrs than reference values (42). These parameters worsened till abnormal if the child was symptomatic suggesting that measurements outside the normal range may reveal a clinical deterioration (42). However, the technique failed to distinguish CF subjects from controls (43) and multiple measurements over one year did not correlate with the worsening of the disease described as airway inflammation, pathogens in the BAL and structural changes at the CT (44). When IOS was used in a group of patients with CF including children aged >3 years, R, Fres and AX values increased during exacerbation and decreased after treatment, while X (10-15 Hz) values decreased during exacerbation and increased after recovery (45). However, when compared with spirometry, IOS was not as sensitive as spirometry to detect and follow in the long-term lung function deterioration (46).

Only a few studies measured Rrs and Xrs in young children born preterm, showing less compliant airways as demonstrated by abnormal values of resistance and reactance (16, 47, 48) that were particularly altered in those with BPD (16, 27). Furthermore, airway resistance correlated with oxygen therapy duration (47). Higher resistance R5 and R10, and also lower reactance X5 in those exposed to passive smoke, were found in preschool children born late preterm (49).

In summary, FOT seems to be more useful for showing differences between groups of patients rather than for following a disease (11). There is a large variability of Zrs in healthy preschool-age children and several reference equations have been published (3, 11).

Preschool spirometry

Spirometry is the gold standard technique to measure lung function in children aged ≥6 years and adults. In preschool age the forced manoeuvre requires good collaboration and coordination to sustain the effort throughout the expiration and obtaining reliable results can be difficult and time-consuming. That said, several studies report successful spirometry measurements in preschool children (50-52). Criteria for acceptability in this age group are at least two good flow-volume curves with a rapid rise to peak flow and a smooth descending limb with no evidence of cough or glottic closure (3). In this age range a total expiration time of 0.5 ($FEV_{0.5}$) or 0.75 ($FEV_{0.75}$) seconds can be accepted (3), because only 41-75% of children younger than 4 years are able to produce a good FEV_1 (50, 53). Indications for $FEV_{0.5}$ value interpretation have been reported (52, 54). The GLI equations include reference equations for preschool children since 3 years of age and also predictive equations for $FEV_{0.75}$ (55).

In young children with wheeze spirometry impairment vary among the studies. In a big population study set in Seoul, children with recurrent wheeze had lower FEV_1/FVC and FEF_{25-75} than healthy controls [56]. In Argentinian children aged 3-5 years FVC and $FEV_{0.75}$ were significantly lower than those of healthy peers (57). In the U-Biopred cohort spirometry did not detect any difference in lung function between preschool children with severe and mild/moderate wheeze arguing that FEV_1 is a poor index of disease severity (58). When spirometry is used to assess response to bronchodilators there is little evidence that it can be used in wheezing preschool children (59), but the greatest BDR is usually seen in those who are at more risk for a diagnosis of asthma in later age (60). A change in $FEV_{0.75}$ of 11% has been suggested as cut-off to distinguish preschool children with asthma (57).

Children with CF have been followed-up longitudinally using spirometry and most of the studies demonstrate that their lung function is already compromised at preschool age in up to 36% of subjects (61-64). Furthermore, the presence of a bacterial pathogen such as Pseudomonas aeruginosa or Staphylococcus aureus in the airways was associated with a reduction in $FEV_{0.75}$ ranging between 11.3% and 15.6%

(65). However, the abnormalities are often mild and sometimes not detectable, but when assessed longitudinally FEV_1 shows an inverse relationship with the more sensitive parameter lung clearance index (LCI) (66). Spirometry was also recently used in preschoolers with CF to assess the effect of a trial with hypertonic saline and showed improved FVC values after 16 weeks of treatment and decreased FEV_1 and FEF_{25-75} in the group on normal saline. In the same study Rint did not detect any effect (67).

In preschool children born preterm, in whom the tracking of lung function might be very useful, the clinical application of spirometry is complicated by the possible cognitive impairment that sometimes is associated with prematurity. In a recent paper on children born extremely preterm including also children aged 4-5 years only 46% of the population was able to complete a full spirometry manoeuvre resulting in an acceptable FVC (48). Despite this, the results showed an impaired lung function in terms of FVC and FEV_1 compared to controls born at term.

Overall, the published studies on measurement of lung function with spirometry in preschoolers show that the test is safe, feasible and reproducible especially if performed by experienced personnel.

Multiple breath washout

The multiple breath washout (MBW) describes the inhomogeneity of ventilation, particularly in the small airways, by measuring the clearance of a gas from the lungs. The test uses an open circuit and is performed at tidal breathing during which a marker gas, usually nitrogen, is washed out with 100% oxygen. The washout continues until gas concentration has reached levels lower than 1/40 of the initial concentration (3, 68).

Preschool children perform the test in a seated position and a video can be used for distraction and to promote a regular breathing pattern. Minimal cooperation and coordination are required; the test showed a feasibility of 91% in preschool children (85% under 4 years) (69). LCI, moment ratios and the conductive and acinar ventilation heterogeneity (Scond and Sacin) are some of the parameters used to measure ventilation inhomogeneity. Functional residual capacity (FRC) and the dead space of the conducting airways can also be obtained. LCI is the principal measure considered in MBW and the value most used to interpret the test in clinical practice. LCI is calculated as the number of lung volume turnovers required to clear the lungs of the marker gas to 1/40th of the starting concentration (3, 68). A higher LCI value indicates greater ventilation inhomogeneity and therefore greater disease severity.

Increased LCI and Scond values were found in preschool children with multiple-trigger wheeze compared with episodic viral wheeze and healthy control subjects. In this cohort 39% and 68% of the subjects with multiple-trigger wheeze had abnormal values of LCI and Scond respectively (70). In a recent paper only Scond discriminated preschool children with asthma from healthy controls but the sample was smaller and in asthmatic subjects FeNO was normal maybe suggesting a less severe disease (69). Normal values of LCI were found also in a group of 32 children with asthma including subjects in preschool age but when compared to healthy peers they had slightly higher values (71). These results are concordant with those reported in adults where even in patients with mild asthma LCI is often normal, while the most consistent evidence of ventilation inhomogeneity is in the conducting airways (72). In an interesting paper by Sonnappa et al. MBW was used to evaluate lung function in preschool wheezers who previously had increased reticular basement membrane (RBM) thickness and increased airway eosinophils. The group showed significantly higher median LCI and Scond than healthy controls but these results did not correlate with past RBM thickness or mucosal eosinophilia (73). The only parameter that showed a significant BDR was Scond but just 16% of wheezy children showed a response larger than the determined threshold (73).

In preschool children with CF LCI is consistently elevated (74). LCI value has been shown to be more sensitive than FEV_1 for detecting alterations of peripheral airways (75) and data support its capacity in the recognition of early lung disease and in the prediction of lung function at school age (74, 76). When MBW was performed at different time points, LCI increased in preschool children with CF over 1 year and worsened during pulmonary exacerbations suggesting that this parameter can track the progression of the disease and can be used to monitor these young patients (66, 77). Because of its sensitivity, MBW might be used to assess the effect of pharmacological treatment in patients with chronic lung disease. In one interventional study in young children with CF, LCI measured, at baseline and after a trial of 48 weeks with hypertonic saline 7% significantly improved (i.e. decreased) compared to the value measured in subjects on isotonic saline 0.9% (78). LCI has also been found to be sensitive in detecting the improvement in ventilation homogeneity 1 month after the antibiotic therapy taken during a pulmonary exacerbation (79). Furthermore, in the same study LCI values correlated with the magnetic resonance scores used to describe lung abnormalities (79).

To our knowledge there are no reports on MBW during preschool age in children born preterm.

The clinical usefulness and the applicability of MBW in the daily care of the patient and in the decision of which treatment apply still need to be defined because there are gaps in the choice of the device and in the standardization of the technique across the different systems. However, LCI may be a valuable tool to investigate ongoing symptoms or as an outcome in clinical research studies (80). At present MBW is not routinely used in clinical practice but in centers where this technique is regularly performed an increase of 1 unit in the LCI value is considered a sign of pulmonary deterioration (82). As shown in the only published reference equations, LCI is dependent on body size and decreases as height increases, particularly in early childhood. Therefore, the upper limit of normal LCI is higher in infants and preschool children than in older subjects (81).

Conclusions

In conclusion, Rint, FOT, spirometry and MBW are feasible and reproducible in preschoolers. They have a role in identifying changes in airway calibre and compliance and are potentially very useful in the clinical assessment and follow-up of a child with respiratory disease. To confirm their applicability and capability in tracking lung function over time further studies on the short and long-term utility of these techniques are needed.

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