Is forced oscillation technique the next respiratory function test of choice in childhood asthma

Afaf Alblooshi, Alia Alkalbani, Ghaya Albadzi, Hassib Narchi, Graham Hall

Afaf Alblooshi, Ghaya Albadzi, Hassib Narchi, Department of Pediatrics, United Arab Emirates University, Al-Ain, United Arab Emirates

Alia Alkalbani, Department of Pediatrics, Tawam Hospital, Al-Ain, United Arab Emirates

Graham Hall, Department of Children’s Lung Health, Telethon Kids Institute, Perth 6000, Australia

Graham Hall, School of Physiotherapy and Exercise Science, Curtin University and Centre of Child Health Research, University of Western Australia, Perth 6000, Australia

Author contributions: Alblooshi A developed the framework for the review; Alblooshi A and Alkalbani A wrote the manuscript with guidance; Narchi H and Hall G designed overall direction from; all authors contributed to the final version of the manuscript.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Afaf Alblooshi, Professor, Department of Pediatrics, United Arab Emirates University, P.O. Box 17666, Al-Ain, United Arab Emirates. afaf.alblooshi@uaeu.ac.ae

Telephone: +971-3-7137433
Fax: +971-3-7672022

Received: February 27, 2017
Peer-review started: February 28, 2017
First decision: September 4, 2017
Revised: October 8, 2017

Accepted: November 1, 2017
Article in press: November 1, 2017
Published online: December 26, 2017

Abstract

Respiratory diseases, especially asthma, are common in children. While spirometry contributes to asthma diagnosis and management in older children, it has a limited role in younger children whom are often unable to perform forced expiratory manoeuvre. The development of novel diagnostic methods which require minimal effort, such as forced oscillation technique (FOT) is, therefore, a welcome and promising addition. FOT involves applying external, small amplitude oscillations to the respiratory system during tidal breathing. Therefore, it requires minimal effort and cooperation. The FOT has the potential to facilitate asthma diagnosis and management in pre-school children by facilitating the objective measurement of baseline lung function and airway reactivity in children unable to successfully perform spirometry. Traditionally the use of FOT was limited to specialised centres. However, the availability of commercial equipment resulted in its use both in research and in clinical practice. In this article, we review the available literature on the use of FOT in childhood asthma. The technical aspects of FOT are described followed by a discussion of its practical aspects in the clinical field including the measurement of baseline lung function and associated reference ranges, bronchodilator responsiveness and bronchial hyper-responsiveness. We also highlight the difficulties and limitations that might be encountered and future research directions.

Key words: Asthma; Forced oscillation technique; Impulse oscillatory; Pre-school; Children; Pulmonary function test

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.
Core tip: Respiratory diseases, such as asthma, are especially common in children. Although their diagnosis and management are facilitated by using spirometry in older children, the use of the latter remains limited in younger children because of their inability to perform forced expiratory manoeuvre. Therefore, the use of new methods which require minimal effort and cooperation from children, such as the forced oscillation technique (FOT) is a welcome and promising addition to identify children with underlying airway function abnormalities. In this article, we review the available literature on the use of FOT in childhood asthma.

INTRODUCTION

Asthma is the most common chronic childhood disease worldwide. It is often difficult to diagnose in infants and young children due to lack of objective measures, such as spirometry. Spirometry is the gold standard method to assess lung function in older children and adults. However, obtaining acceptable and repeatable spirometry measures requires significant efforts and high level of cooperation. Therefore, the diagnosis and management of childhood asthma remain suboptimal, in young children and older children who cannot perform an acceptable forced expiratory manoeuvre.

One potential lung function method suitable for use in young children and older children unable to perform spirometry is the forced oscillation technique (FOT). The FOT was developed by DuBois et al. in 1956, to measure the mechanical behaviour of the respiratory system. Over the years, the FOT has been used in research and more recently in clinical practice. The application of FOT has expanded to the point where commercial equipment are now widely available. Standardized approaches for the collection of FOT outcomes have been established by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) in pre-school children.

One significant advantage of the FOT is its application during tidal breathing and the subsequent reduction in the level of active participation and cooperation required from the individual being tested. As a result, this technique can be feasibly used in children as young as two years of age. Consequently, the FOT opens new frontiers in the application of objective measurements of respiratory function in young children and offers improvements in the diagnosis and management of asthma in young children.

In this review we have summarised the available literature on the use of FOT in childhood asthma. The technical aspects of FOT are briefly described followed by a discussion of its practical aspects in the clinical field, including the measurement of baseline lung function and associated reference ranges, bronchodilator responsiveness and bronchial hyper-responsiveness. We also highlight the difficulties and limitations that might be encountered and future research directions.

Technical aspects of FOT

The basic principle of FOT involves the application of external signals into the respiratory system and measuring the resulting response of that system. This response is termed the respiratory system impedance (Zrs). The Zrs can be determined when flow and pressure are measured across a known frequency range at the airway opening and is represented as the resistance (Rrs) and reactance (Xrs) of the respiratory system.

\[
Z_{rs} = P_{ao} / V'_{ao} = R_{rs} + jX_{rs}
\]

where \(P_{ao}\) is the pressure \(V'_{ao}\) is the flow measured at the airway opening and \(j = \sqrt{-1}\).

Resistance (Rrs) represents the component of Zrs that is a function of both \(P_{ao}\) and \(V'_{ao}\), equating to the resistive properties of the respiratory system. Reactance (Xrs) is the out-of-phase component that is a function of both \(P_{ao}\) and volume, reflecting elastic recoil of the respiratory system. Both Rrs and Xrs are determined when oscillatory (sound waves) signals are applied at the airway opening (and hence to the whole respiratory system).

It is important to be aware that the respiratory impedance is frequency-dependent: (1) At low frequencies, (2-4 Hz) as the oscillations are transmitted more distally into the lungs, Rrs and Xrs tend to reflect the properties of the peripheral respiratory system; (2) at higher frequencies, (> 20 Hz) the Zrs reflects the resistive and inertive properties of the proximal conducting airways.

It is critical to note that Rrs and Xrs reflect mechanical properties of the entire respiratory system, including the airway, lung and chest wall. It is therefore not possible to assign specific anatomical changes (for example central airway obstruction) to changes in any one FOT outcome at a specific frequency (see below for further details).

As the airway and the lung tissue are both flow and volume-dependant, the characteristic of the oscillatory signals used is important. These signals can take any of the following common forms: (1) Single frequency; (2) impulse oscillation system; (3) pseudorandom noise (the simultaneous application of several frequency components).

The oscillation signal that is most commonly applied encompasses the medium frequency range, generally including frequencies between 2 Hz and 20 Hz. The advantage of using mid-range frequencies is that the oscillatory signals can be superimposed on the tidal breathing and therefore result in a broader application. For more details reviews on the technical aspects of FOT, readers are directed to review (oscillation mechanics of respiratory system) by Bates et al.
Practical aspects of FOT
This section summarizes the available equipment, feasibility, repeatability, and finally the collection and reporting of FOT data in young children.

Equipment
The availability of FOT commercial equipment has resulted in the increased uptake of FOT in clinical practice and especially in young children. The FOT equipment includes (Figure 1): (1) A loudspeaker or similar to generate the oscillatory signals; (2) a pneumotachograph and pressure transducers to measure pressure and flow; (3) a mouth piece containing a bacterial filter to prevent cross infection between patients. A typical arrangement of the forced oscillatory impedance measurement, adapted from [9].

Feasibility
The feasibility and success rates of FOT are, understandably, age-dependent. The success rate in children 4 years of age and older exceeds 80% [13,16,17], while it ranges from 83% to 100% in healthy children aged 2-7 year [13,18] and between 57% to 100% in children with asthma aged between 3 to 5 years [13,16]. In young children with acute asthma the success rate of FOT reduced to 24% and 65% in three and eight-year-old children respectively, however, it was higher than that of spirometry in the same population [12]. Furthermore, the feasibility of FOT measurements increases noticeably with practice in children.

The feasibility of FOT with challenge testing has been assessed in several research studies and has been shown to be feasible in young children using either inhaled adenosine monophosphate (AMP) [19], free running [20], methacholine [21-23], hypertonic saline [21], cold air [24] or mannitol challenge [25].

Collection of FOT data
For adequate collection of the data, the child should be seated with their back straight and their neck either in the neutral position or slightly extended. FOT is usually performed with the mouthpiece which incorporates a bacterial filter and a nose clip-on. A staff member or a parent needs to support the child’s cheeks as well as the floor of his mouth, as shown in Figure 2. An acquisition period should cover several breathing cycles, typically lasting 8-16 s. The results, computed as the mean value of the three to five acceptable measurements, also include the measurement of the coefficient of variation calculated from the standard deviation (SD) of the measurements. Acceptable measures are the one which have no artefacts such as leak, incomplete expiration, glottis closure, swallowing and the child obstructing the mouthpiece with their tongue are easily identified [9] (Figure 2).

Repeatability
Repeatability is an important issue when considering the role of a lung function measures. The short-term repeatability of FOT in healthy children has been assessed and it is summarized in Table 1 below. The long term (two weeks) and short term repeatability were both similar [19].

Reporting and interpreting FOT data
Commonly reported FOT outcomes include resistance (Rrs), reactance (Xrs) at different frequencies, resonance frequency (Fres), frequency dependence (Fdep), and the area under reactance curve (AX), as illustrated in Figure 3. The reported Rrs variable includes, in the same measurement, the Rrs of the airway, that of the chest wall, and that of the lung tissue. As airway Rrs dominates Rrs in the mid frequencies [26], it can be considered a surrogate of airway resistance [27,28]. As frequency decreases to below approximately 4 Hz Rrs will increasing include peripheral respiratory resistance and be reflective of the peripheral airways and the lung. As Xrs, on the other hand, is dominated by elastic properties of the respiratory tissue, reflecting the elastic
frequency at which elastive and inertive properties of the lung are balanced, and which becomes positive at higher frequencies\textsuperscript{[30]}. The Fdep of that resistance is thought to reflect peripheral airway resistance\textsuperscript{[31]}, as, for example, in patients with obstructive airway diseases, it is generally higher than normal subjects due to the difference in airway resistance\textsuperscript{[30]}. However, to date there are no studies directly confirming this.

The area under the reactance curve (AX) is the sum of the $X_{rs}$ from a $X_{rs}$ at 5 Hz until $F_{res}$ (i.e., when $X_{rs}$ is zero, as in Figure 3)\textsuperscript{[29]}. Studies have shown that $X_{rs}$ and AX are better representative of peripheral airway obstruction than $R_{rs}$\textsuperscript{[29]} and that AX and Fres clearly

| Author         | Year | $n$ | $R_{rs}$ | $X_{rs}$ |
|----------------|------|-----|----------|----------|
| Hall et al\textsuperscript{[13]} | 2007 | 58; field | $\sim 2$ or $\sim 30\%$ | 1.2 - 1.7 |
| Malmberg et al\textsuperscript{[18]} | 2002 | 19; placebo | 1.1 or $\sim 12\%$ | 1.3 |
| Klug et al\textsuperscript{[16]} | 1998 | 120 | 2.6 or $\sim 20\%$ | 2 |

$R_{rs}$: Respiratory system resistance; $X_{rs}$: Respiratory system reactance (in $hPa/s$ per L).
distinguish healthy children from those with small airway disease and asthma[32].

The FOT outcomes alter with growth and therefore need to be reported as both absolute values and as a function of a predicted value. Expressing outcomes as z or SD scores is the most appropriate. Z scores allows the easy estimation of the lower limit of normal (being either -1.64 or -1.96) and avoids the diagnostic uncertainly that can arise when using percent predicted and a fixed cut off for the presence of abnormal lung function[33,34].

Reference range of FOT measurements
Numerous studies have reported reference data in healthy children using a variety of FOT outcomes[13,35-44]. The FOT outcomes are generally reported to change with age, height and gender. There is some variability due to the different ethnicity, gender, age, weight, height, equipment and the methodology used in those studies and it is important that users carefully review potential reference equations to match the populations, equipment and protocols used as closely as possible to their own circumstances[37,45]. Reporting and comparing the relevant z-scores for these measurements simplifies the interpretation as the possible confounders reported earlier have already been taken into consideration when calculating these scores. Table 2 below summarises those studies and shows those differences.

Clinical applications of FOT in children with asthma
By incorporating measurements of bronchodilator Responsiveness (BDR) and bronchial hyper-responsiveness (BHR), the utility of FOT to assist in the diagnosis of asthma in young children may be increased[47]. The official ATS/ERS statement on pulmonary function testing in preschool children stated that FOT is a promising tool in diagnosing and following up children with asthma[9]. Other studies also suggest that the FOT may be useful in assessing asthma control, compliance to medication, and in the follow up of these young children[48].

Baseline FOT and the severity of asthma
In children aged 5 years and above, spirometry adequately assesses baseline lung function and the results correlate well with asthma severity[49]. When comparing spirometry and FOT in children older than 6 years of age, those with asthma have lower baseline FOT than with spirometry when compared to healthy children[50]. Whilst few studies have examined baseline airway obstruction in young children with asthma using FOT. Klug et al[51] reported that young children with stable asthma demonstrated impaired baseline lung function when assessed using FOT. Oostveen et al[17] showed that, when compared to healthy 4-year-old children,
those children with persistent wheeze had worse baseline lung function than those with transient wheeze as assessed by FOT. Children with a history of recurrent wheeze and/or asthma recruited from clinics tend to have worse lung function expressed in FOT even when asymptomatic\cite{18,52}. However, other studies conducted in children with history of wheeze and recruited from the community have similar FOT outcomes to healthy children\cite{53,54}. The ability of FOT to determine asthma severity remains therefore questionable, especially in children on asthma medication\cite{49}. Further studies are therefore needed to explore the relationship between baseline lung function using FOT and asthma severity in young children with asthma.

### Bronchodilator response using FOT

The assessment of bronchodilator responsiveness using FOT in young children with asthma has been encouraged in clinical practice\cite{10}. Critical the the assessment of increased responsiveness associated with asthma is an understanding of the response of healthy children with bronchodilators. The assessment of change in FOT outcomes during the assessment of BDR has been expressed as absolute change or relative change from the baseline in the Rsrs, Xrs and AX, the use of AX has been explored in a few studies and is shown to be a good outcome in assessing the BDR in children with asthma\cite{17,26,32}.

In the most recent study which assessed BDR in children (Calogero et al\cite{53}), cut-offs for a positive BDR in healthy Caucasian children were defined as 34% and 50% for Rsrs and Xrs, respectively expressed as a relative change from the baseline lung function. In a study looking at the uses of pseudorandom FOT signal (4–48 Hz) in quantifying BDR in healthy young children, children with cysitic fibrosis, neonatal chronic lung disease and children with asthma and/or current wheeze, Thamrin et al\cite{53} recommended a positive BD response of 40% and 65% for Rsrs and Xrs, respectively expressed as a relative change from the baseline lung function\cite{53}. Another study, conducted by Oostveen et al\cite{17} in Belgium on 4 years old healthy and wheezy children (n = 325) using FOT, recommended a positive BDR at Rsrs 4 of 43% expressed as absolute changes. Cut-off values for BDR in previous studies are summarized and listed in Table 3. In general, > 30% decrease in Rsrs after bronchodilator is suggestive of asthma.

The previous studies in healthy and wheezy young children have not conducted a ROC analysis to formally establish the sensitivity and specificity of a certain BDR cut off to be assessed. Limitations to the wider use of FOT in assessing BDR include the variability of medications, their timing and dosage between the different studies (Table 3).

### Bronchial hyper-responsiveness using FOT

Bronchial hyper-responsiveness, usually assessed using spirometry, is the gold standard for confirming a diagnosis of asthma in older children and adults\cite{58,59}. However, false negative or false positive results can occur in young children who cannot perform an acceptable manoeuvre. BHR has been assessed in young children using other methods including FOT, interrupter technique, whole-body plethysmography and transcutaneous oxygen measurement SPO$_2$\cite{5,47,60-63}.

Bronchial hyper-responsiveness studies comparing FOT with different lung function measures have reported FOT to be as effective as spirometry\cite{63-69} and as sensitive as body plethysmography\cite{70} and transcutaneous PO$_2$\cite{50} in older children with asthma. BHR has been assessed using FOT in children younger than 7 years of age with a range of challenge tests including adenosine monophosphate (AMP)\cite{18,24}, cold air\cite{21}, normal saline\cite{21}, metacholine\cite{20,62,63,66,67,71}, mannitol\cite{75} and exercise\cite{35,72} demonstrating that FOT can be reliably used in young children for challenge testing.

FOT characterization of BHR has shown to be correlated to asthma severity\cite{73} and to be sensitive to the response to immune therapy\cite{74}. Another study has shown that cough variant asthma showed less BHR in comparison to classical asthma children\cite{75}.

Despite the above studies have clearly demonstrated the use of FOT to assess BHR in children, there are few studies demonstrating the best cut off value of BHR between healthy and children with asthma using FOT. Further work is needed before establishing FOT use as clinical tool to assess BHR in children.

### Limitation of FOT in children and future direction

Although forced oscillation technique can contribute to the diagnosis and management of childhood asthma, it has some limitations. Although, unlike spirometry, it does not require forced expiratory manoeuvres, it still require some cooperation by children to achieve successful repeatable measures. It is therefore both age and cooperation dependant. The practical advantage of the availability and affordability of different FOT commercial equipment, the Rsrs and Xrs output are not always measured at the same frequencies by all these devices. This makes the comparison between different studies challenging. The standardization of the available commercial equipment is therefore still needed and FOT guidelines are currently being reviewed by the ATS and ERS.

As the available FOT reference equations have been constructed in specific populations, these findings cannot be generalised to other ethnic groups. Further studies are therefore still required to establish FOT reference values in other populations or ethnic groups. The assessment of BDR using FOT is not widely implemented because of differences amongst the relevant studies, including differences in the medications used, as well as their timing and dosage. Further studies are therefore required to establish an international standard protocol for this assessment as currently BDR still has not been studied in relation to recent symptoms in young children with wheeze, developing such studies.
would help not only in the follow up of children with wheeze, but also to ascertain the level of control of asthma symptoms and the compliance to medication in children with asthma.

Further research is also required to assess BHR, particularly in young children, in addition to standardise the use of FOT in young children for BHR assessment.

Recently there are new studies that have reported Rs or Xrs from either expiration or inspiration (or both), including flow limitation within a breath. Those studies suggest that this approach is more sensitive than standard reporting of FOT. However, significant work is required prior to the introduction of these outcomes into clinical practice and this remains an area for the future studies\textsuperscript{(6,77)}.

In conclusion, with the relatively high prevalence of childhood asthma, FOT has been proven to be a useful tool to aid in its diagnosis and management especially in children unable to perform spirometry. As the recent availability of commercial equipment has increased its tool to aid in its diagnosis and management especially in children unable to perform spirometry. As the recent availability of commercial equipment has increased its use both in research and in clinical practice, clinicians have to understand the emerging role of FOT in clinical practice and how to interpret its results in order to optimise clinical management of children with asthma.

### REFERENCES

1. Braman SS. The global burden of asthma. *Chest* 2006; 130: 4S-12S
2. Patterson PK, Asher MI, Harrison AC, Mitchell EA, Rea HH, Stewart AW. The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma, and asthma symptoms. *Am Rev Respir Dis* 1990;142: 549-554 [PMID: 2202246 DOI: 10.1164/ajrccm/142.3.549]
3. Mai XM, Nilsson L, Kjellman NI, Björkstén B. Hypertonic saline challenge tests in the diagnosis of bronchial hyperresponsiveness
and asthma in children. *Pediatric Allergy Immunol* 2002; 13: 361-367 [PMID: 12431196]

4 Global Initiative for Asthma. Global strategy for asthma management and prevention 2017. Available from: URL: http://www.ginasthma.org

5 Kanemitsu S, Doxor AJ. Forced expiratory maneuvers in children aged 3 to 5 years. *Pediatric Pulmonol* 1994; 18: 144-149 [PMID: 7800430]

6 Crepesi D, Berlioz M, Bourrier T, Albertini M. Spirometry in children aged 3 to 5 years: reliability of forced expiratory maneuvers. *Pediatric Pulmonol* 2001; 32: 56-61 [PMID: 11416877]

7 Arets HG, Brackel HJ, van der Ent CK. Forced expiratory maneuvers in children: do they meet ATS and ERS criteria for spirometry? *Eur Respir J* 2001; 18: 655-660 [PMID: 11716170]

8 Dubois AB, Botelho SY, Comoro 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: 327-335 [PMID: 13295397 DOI: 10.1172/jci032282]

9 Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, Gappa M, Gauthier C, Gustafsson PM, Hall GL, Hantos Z, Healy MJ, Jones MH, Klug B, Lodrup Carlsen KC, McKenzie SA, Marchal F, Mayer OH, Merkus PJ, Morris MG, Oostveen E, Pillow JJ, Seddon PC, Silverman M, Sly PD, Stocks J, Tepper RS, Vilozni D, Wilson NM; American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing. 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 [PMID: 17545458 DOI: 10.1164/rcrm.200605-642ST]

10 Oostveen E, MacLeod D, Lorino H, Farry R, Hantos Z, Desager K, Marchal F; ERS Task Force on Respiratory Impedance Measurements. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003; 22: 1026-1041 [PMID: 14680096]

11 Marchal F, Hall GL. Forced oscillation technique. Paediatric Lung Function. *European Respiratory Society J* 2010; 47: 121-136 [DOI: 10.1183/09031936.00023409]

12 Ducharme FM, Davis GM. Respiratory resistance in the emergency department: a reproducible and responsive measure of asthma severity. *Chest* 1998; 113: 1566-1572 [PMID: 9631795]

13 Hall GL, Sly PD, Fukashima T, Kusel MM, Franklin PJ, Horak F Jr, Patterson H, Gangell C, Stick SM. Respiratory function in healthy young children using forced oscillations. *Thorax* 2007; 62: 521-526 [PMID: 17253135 DOI: 10.1136/thx.2006.067835]

14 Davis SD, Elber E, Kounbilaris AC. Applications and Interpretation of the oscillometry using a body plethysmograph. *Respir Physiol Neurobiol* 2014: 161-162 [DOI: 10.1016/j.resp.2014.01.001]

15 Bates JH, Irvin CG, Farré R, Hantos Z. Oscillation mechanics of the respiratory system. *Compr Physiol* 2011; 1: 1233-1272 [DOI: 10.1002/cphy.c100058]

16 Klug B, Bisgaard H. Specific airway resistance, interrupter resistance, and respiratory impedance in healthy children aged 2-7 years. *Pediatric Pulmonol* 1998; 25: 322-331 [PMID: 9635934]

17 Oostveen E, Dom S, Desager K, Hagedoorns M, De Backer W, Weyler J. Lung function and bronchodilator response in 4-year-old asthmatic children during methacholine challenge and acute asthma: a comparison of the impulse oscillation technique, the interrupter technique, and transcutaneous measurement of oxygen versus whole-body plethysmography. *Pediatr Pulmonol* 1996; 21: 290-300 [PMID: 8726154 DOI: 10.1002/scti.1099-0496(19960521:53.0.CO;2-R)

18 Nielsen KG, Bisgaard H. Lung function response to cold air challenge in asthmatic and healthy children of 2-5 years of age. *Am J Respir Crit Care Med* 2000; 161: 1805-1809 [PMID: 10852748 DOI: 10.1164/ajrccm.161.6.9905908]

19 Alblooshi AS, Simpson SJ, Stich SM, Hall GL. The safety and feasibility of the inhaled mannitol challenge test in young children. *Eur Respir J* 2013; 42: 1420-1423 [PMID: 23985769 DOI: 10.1183/09031936.0041713]

20 FREY U. Forced oscillation technique in infants and young children. *Paediatr Respir Rev* 2005; 6: 246-254 [PMID: 16298307 DOI: 10.1016/j.prrv.2005.09.010]

21 Bates JH, Daroncy B, Hantos Z. A comparison of interrupter and forced oscillation measurements of respiratory resistance in the dog. *J Appl Physiol* (1985) 1992; 72: 46-52 [PMID: 1537743]

22 Jackson AC, Tennhoff W, Kramer R, Frey U. Airway and tissue resistance in wheezy infants: effects of albuterol. *Am J Respir Crit Care Med* 1999; 160: 557-563 [PMID: 10430728 DOI: 10.1164/ajrccm.160.2.9808137]

23 Goldman MD, Saadeh C, Ross D. Clinical applications of forced oscillation to assess peripheral airway function. *Respir Physiol Neurobiol* 2005; 148: 179-194 [PMID: 15990365 DOI: 10.1016/j.resp.2005.05.026]

24 Grimby G, Takashima T, Graham W, Macklem P, Mead J. Frequency dependence of flow resistance in patients with obstructive lung disease. *J Clin Invest* 1968; 47: 1455-1465 [PMID: 5653219 DOI: 10.1172/JCI105837]

25 Goldman MD. Clinical application of forced oscillation. *Palm Pharmacol Ther* 2001; 14: 341-350 [PMID: 11609348 DOI: 10.1006/pupt.2001.0310]

26 Merz E, Nazeran H, Goldman M, Nava P, Diong B. Impulse oscillometric features of lung function: towards computer-aided classification of respiratory diseases in children. *Conf Proc IEEE Eng Med Biol Soc* 2008; 2008: 2443-2446 [PMID: 19163196 DOI: 10.1109/embs.2008.469693]

27 Stanoev J, Wade A, Lind S, Stocks J. Reference equations for pulmonary function tests in preschool children: a review. *Pediatric Pulmonol* 2007; 42: 962-972 [DOI: 10.1002/ppd.20691]

28 Stanoev J, Wade A, Stocks J. Reference values for lung function: past, present and future. *Eur Respir J* 2010; 36: 12-19 [DOI: 20595163 DOI: 10.1183/09031936.00413209]

29 Frei J, Junta J, Kramer G, Hatzakis GE, Ducharme FM, Davis GM. Reference values for respiratory system impedance by using impulse oscillometry in children aged 2–11 years. *Chest* 2005; 128: 1266-1273 [DOI: 10.1378/chest.128.3.1266]

30 Dencker M, Malmberg LP, Valind S, Karlsson MK, Pelkonen A, Pohjanpalo A, Haataela T, Turpeinen M, Wolterm P. Reference values for respiratory system impedance by using impulse oscillometry in children aged 2-11 years. *Clin Physiol Funct Imaging* 2006; 26: 247-250 [PMID: 16836699 DOI: 10.1111/j.1475-097X.2006.00682.x]

31 Amra B, Soltaninejad F, Golshan M. Respiratory resistance by impulse oscillometry in healthy Iranian children aged 5-19 years. *Iran J Allergy Asthma Immunol* 2008; 7: 25-29 [PMID: 18322309 DOI: 07:01/ijai/2529]

32 Nowowiejska B, Tomala W, Radliński J, Siergiejko G, Latawiec W,
impedance and response to salbutamol in asthmatic Vietnamese children. Pediatr Pulmonol 2010; 45: 380-386 [PMID: 20306537 DOI: 10.1002/ppul.20940]

Calogero C, Patni N, Baccini A, Cuomo B, Palumbo M, Novembrini E, Morello P, Azzari C, de Martino M, Sisto PD, Lombardi E. Respiratory impedance and bronchodilator response in healthy Italian preschool children. Pediatr Pulmonol 2010; 45: 1086-1094 [PMID: 20672294 DOI: 10.1002/ppul.21292]

Park JH, Yoon JW, Shin YH, Jee HM, Wex YS, Chang SJ, Sim JH, Yum HY, Han MY. Reference values for respiratory system impedance using impulse oscillometry in healthy preschool children. Korean J Pediatr 2011; 54: 64-68 [PMID: 21503199 DOI: 10.3345/kjp.2011.54.2.64]

Calogero C, Simpson SJ, Lombardi E, Patni N, Cuomo B, Palumbo M, de Martino M, Shackleton C, Verheggen M, Gavidia T, Franklin PJ, Kusel MM, Park J, Sly PD, Hall GL. Respiratory impedance and bronchodilator responsiveness in healthy children aged 2-13 years. Pediatr Pulmonol 2013; 48: 707-715 [PMID: 23169525 DOI: 10.1002/ppul.22699]

Shackleton C, Barraza-Villarreal A, Chen L, Gangell CL, Romieu I, Sly PD. Reference ranges for Mexican preschool-aged children using the forced oscillation technique. Arch Bronconeumol 2013; 49: 326-329 [PMID: 23587799 DOI: 10.1016/j.arbes.2013.01.014]

Frei J, Jutla J, Kramer G, Hatzakis GE, Ducharme FM, Davis GM. Impulse oscillometry: reference values in children 100 to 150 cm in height and 3 to 10 years of age. Chest 2005; 128: 1266-1273 [PMID: 16162717]

Hagiwara S, Mochizuki H, Muramatsu R, Koyama H, Yagi H, Nishida Y, Kobayashi T, Sakamoto N, Takizawa T, Arakawa H. Reference values for Japanese children’s respiratory resistance using the LMS method. Allergol Int 2014; 63: 113-119 [PMID: 24569154 DOI: 10.2332/allergolint.13-OA-0591]

Bisgaard H, Klug B. Lung function measurement in awake young children. Eur Respir J 1995; 8: 2067-2075 [PMID: 8666102]

Shi Y, Aledia AS, Galant SP, George SC. Peripheral airway impairement measured by oscillometry predicts loss of asthma control in children. J Allergy Clin Immunol 2013; 131: 718-723 [PMID: 23146378 DOI: 10.1016/j.jaci.2012.09.022]

Bacharier LB, Strunk RC, Maurer D, White D, Lemanske RF Jr, Strunk RC, Jörres R, Berdel D, Làndsér FJ. Correspondence between bronchodilator response slope. Pediatr Pulmonol 2014; 49: 521-528 [PMID: 24039248 DOI: 10.1002/ppul.22866]

Peták F, Czókev D, Novák Z. Spirometry and forced oscillations in the detection of airway hyperreactivity in asthmatic children. Pediatr Pulmonol 2012; 47: 956-965 [PMID: 22451241 DOI: 10.1002/ppul.22551]

Klug B, Bisgaard H. Measurement of the specific airway resistance by plethysmography in young children accompanied by an adult. Eur Respir J 1997; 10: 1599-1605 [PMID: 9230254]

Schulze J, Smith HJ, Fuchs J, Herrmann E, Dressler M, Rose MA, Zienel S. Methacholine challenge test-comparison of reactance and resistance with dose-response slope. Pediatr Pulmonol 2014; 49: 521-528 [PMID: 24039248 DOI: 10.1002/ppul.22866]

Bailly C, Crenesse D, Albertini M. Evaluation of impulse oscillometry during bronchial challenge testing in children. Pediatr Pulmonol 2011; 46: 1209-1214 [PMID: 21634032 DOI: 10.1002/ppul.21492]

Takami S, Mochizuki H, Muramatsu R, Hagiwara S, Arakawa H. Relationship between bronchial hyperresponsiveness and lung function in children age 5 and 6 with and without asthma. Respir Med 2013; 107: 627-634 [PMID: 23236606 DOI: 10.1016/j.thorax.2012.01.007]

Kim HY, Shin YH, Jung DW, Lee JH, Yoon JW, Han MY. Resistance and reactance in oscillation lung function reflect basal lung function and bronchial hyperresponsiveness respectively. Respiratory Care 2009; 54: 1035-1041 [PMID: 19740263 DOI: 10.1011/ resp.1.12061]

Buhr W, Jörres R, Berdel D, Länsder FJ. Correspondence between forced oscillation and body plethysmography during bronchoprovocation with carbachol in children. Pediatr Pulmonol 1990; 8: 280-288 [PMID: 2196514]

Jee HW, Kwak JH, Jung DW, Han MY. Usefull parameters of bronchial hyperresponsiveness measured with an impulse oscillation
technique in preschool children. *J Asthma* 2010; 47: 227-232 [PMID: 20394507 DOI: 10.3109/02770901003624259]

72 **Schweitzer C**, Abdelkarim IB, Ferry H, Werto F, Varechova S, Marchal F. Airway response to exercise by forced oscillations in asthmatic children. *Pediatr Res* 2010; 68: 537-541 [PMID: 20736883 DOI: 10.1203/PDR.0b013e3181f51d2]

73 **Wang JY**. The study of bronchial hyperresponsiveness in asthmatic children by forced oscillation technique. *Asian Pac J Allergy Immunol* 1991; 9: 51-56 [PMID: 1776980]

74 **Chen WY**, Yu J, Wang JY. The effect of immunotherapy on bronchial hyperresponsiveness in asthmatic children. *Asian Pac J Allergy Immunol* 1994; 12: 15-20 [PMID: 7872988]

75 **Mochizuki H**, Arakawa H, Tokuyama K, Morikawa A. Bronchial sensitivity and bronchial reactivity in children with cough variant asthma. *Chest* 2005; 128: 2427-2434 [PMID: 16236905 DOI: 10.1378/chest.128.4.2427]

76 **Lombardi E**, Sly P, Parri N, Simpson SJ, Calogero C. Respiratory Impedance Using Forced Oscillation Technique In 3-13 Year-Old Children With A History Of Wheezing. B107 Tools of the trade: modalities for evaluating pediatric lung disease. *Am Thoracic Soc* 2013: A3696

77 **Chacko A**, Czovek D, Mills D, Shackleton C, Hantos Z, Sly PD. Acute Changes In Dynamic Airway Mechanics In Young Children With Viral Wheeze Is Detectable Via Temporal Forced Oscillation Technique. a106 Assessing pediatric lung disease: lung function and beyond. *Am Thoracic Soc* 2015: A2337
