



Airway Oscillometry in Adults and Very Young Children

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Conflicts of interest

- Dr. El Boueiz:
 - None
- Dr. Moschovis:
 - Consultant, Thorasys Thoracic Medical Systems





Small airways disease is highly prevalent in asthma

- Small airways dysfunction and inflammation contribute significantly to the clinical impact of asthma.
- 2016 systematic literature review:
 - Using distinct techniques of small airways assessment
 - Small airways affected in > 50-60% of asthmatics.
 - Small airway disease present across all asthma severities, with evidence of distal airway disease even in the absence of proximal airway obstruction.









Respir Med. 2016;116:19-27.

SAD asthma

- Small-airway dysfunction (SAD) is associated with:
 - Exercise-induced asthma symptoms [OR 6.5 (3.6-11.4)]
 - Asthma-related night awakenings [OR 3.3 (1.8-6.2)]
 - Increased FeNO [OR: 2.0 (1.1-3.7)]
 - Female sex [OR 2.3 (1.3-4.1)]
 - Smoking [OR 3.1 (1.6-6.0)]
 - Older age [OR 3.1 (1.8-5.5)]
 - Overweight [OR 3.6 (2.0-6.8)]
- Though size matters, sometimes even small can outdo the big.



Primarily affects small airways C >>> B > A

J Allergy Clin Immunol Pract. 2020;8(3):997-1004.





Small airways

- Small airways:
 - Are < 2 mm in diameter
 - Are devoid of cartilage and mucous secreting glands
 - Constitute the zone between the conducting and the respiratory lung zones
 - Consist of respiratory and terminal bronchioles
 - Are a major site of pathology in many lung diseases, including asthma and COPD
 - "Zone of silence"? Normally contribute about 10% of the total resistance to flow



Am J Respir Crit Care Med 1998;157:S181-S183. J. Appl. Physiol. 27(3):328-335.





Large vs. small airways

Large airways

- Less cross sectional area
- Turbulent flow
- Resistance affected by gas density
- No surfactant lining over the epithelium

Small airways

- Larger cross sectional area
- Laminar flow
- Gas density has no effect on resistance
- Surfactant lining and hence low surface tension



Am J Respir Crit Care Med 1998;157:S181-S183. *J. Appl. Physiol.* 27(3):328-335.





Assessment of small airways

• Small airways have proven difficult to study due to their relative inaccessibility to biopsy and their small size which makes their imaging difficult.

	Outcome	Measures
Spirometry	Dynamic volumes and flow	FEF ₂₅₋₇₉ , ratio of forced vital capacity to relaxed vital capacity*
Single-breath and multiple-breath nitrogen washout	Air trapping and ventilation heterogeneity	Functional residual capacity, ratio of closing volume to vital capacity, ratio of residual volume to total lung capacity, S_{acin} , S_{cond}
Impulse oscillometry	Airway obstruction and capacitance	R5-R20, reactance area under curve, reactance at 5 Hz, resonant frequency
Whole-body plethysmography	Airway obstruction and air trapping	R _{and} ratio of residual volume to total lung capacity
Oesophageal balloon	Small airway closure	Closing volume and dynamic compliance
Exhaled-breath nitric oxide	Airway inflammation	Alveolar and bronchial nitric oxide fractions
Imaging	Air trapping and regional distribution	High-resolution CT, gamma scintigraphy, PET, hyperpolarised ³ He MRI
Bronchoscopy	Airway resistance and inflammation	Wedged airway resistance, transbronchial biopsy, bronchoalveolar lavage
Late-phase induced sputum	Airway inflammation	Cell and cytokine profile

Lancet Respir Med. 2014;2(6):497-506.





Spirometry

• FEF₂₅₋₇₅:

- Forced expiratory flow between 25% and 75% of the FVC
- Poor reproducibility as it is dependent on FVC and changes in FVC will affect the portion of the flow-volume curve examined.
- Poor correlation with other markers of small airway disease such as gas trapping and histological evidence of small airway inflammation.
- Alternatives measures (such as FEV₃/FVC, 1-FEV₃/FVC, FVC/SVC, RV, RV/TLC) may have a better accuracy than FEF₂₅₋₇₅, but still suboptimal.



Respir Med. 2019; 156: 58-68.





Airway oscillometry

- Oscillometry refers to a group of techniques for measuring breathing mechanics by superimposing small pressure waves on top of normal tidal breathing.
- 3 main approaches:
 - Forced Oscillation Technique (FOT) single frequency technique
 - Impulse Oscillometry (IOS)
 - Pseudo-Random Noise (PRN)
- Most commercial oscillometry systems use either IOS or PRN











- <u>Loudspeaker</u>: Generates pressure oscillations at various frequencies
- <u>Pneumotach</u>: Has pressure sensors to measure airflow (essential for calculating parameters such as airway resistance and reactance)





Airway oscillometry (AOS)

Slow impulses 5 Hz
 Fast impulses 20 Hz
 High frequencies:

 upper (central) airway

 Low frequencies:

 deep penetration
 total airways (central and peripheral)

Higher oscillation frequencies are reflected from the larger airways Lower frequencies travel more peripherally before returning to the mouth

Frequency-independent change	When resistance values do not vary at different frequencies. If overall resistance is increased, this may be indicative of proximal obstruction.
Frequency-dependent change	When resistance varies with frequency more than age-dependant normal values. This may be indicative of distal obstruction.





AOS advantages

- Requires only passive cooperation of the subject (effortindependent)
 - \checkmark Useful in patients with neuromuscular disease and children
- Sensitive to lung periphery
- Portable
- Easy maintenance
- Easy calibration
- Commercial availability of devices











AOS main limitations

- Lack of reference values
- Lack of extensive evaluation over different disease conditions
- However, these limitations can be overcome once the technique is adopted widely, and more thorough studies are conducted.
- For now, we are using the following Z-scores cutoffs (*Eur Respir J. 2013;42(6):1513-23*):
 - \circ Z-scores < -1.645 indicate that measured value is below the lower limits of normal
 - \circ Z-scores > +1.645 indicate that they are above the upper limits of normal
 - A Z-score of 0 signifies the patient's measurement aligns precisely with the predicted values.





Parameter	Spirometry	FOT/IOS	
Main principle	Flow sensor/volume displacement helps measure flow rates and lung volumes	Forced oscillations of single frequency sound waves (FOT) or impulses of multiple frequency sound waves (IOS) are pushed into the lungs as pressure waves to measure respiratory resistance and reactance	
Main parameters	Volumes: FEV1, FVC	Zrs, Rrs, Xrs, Fres, Ax	
	Flows: PEFR, FEF ₂₅₋₇₅ %		
Patient co-operation required	+++	+	
Type of breathing manoeuvre	Forced exhalation	Tidal breathing	
Variability (intra-subject)	3-5%	5–15%	
Sensitivity to airway location			
Central	+	+++	
Peripheral	++	+++	
Cut off for bronchodilator response	12–15% for FEV1	40% for <i>R</i> ₅ or <i>X</i> ₅	
Cut off for bronchoconstrictor response	20% for FEV1	50% for <i>R</i> 5	
Insight into lung mechanics	+	+++	
Standardised methodology	+++	++	
Availability of robust reference values	+++	+	

 Table 1 Differences between spirometry and FOT/IOS

Breathe 2015 11: 57-65.





Impulse Oscillometry Terminology

Impedance (Xrs)	A calculation of the total force needed to propagate a pressure wave through the pulmonary system, comprising resistance and reactance			
Resistance (R)	Energy required to propagate a pressure wave through the airways; to pass through the bronchi and bronchioles, and to distend the lung parenchyma. Resistance is determined when a pressure wave is unopposed by airway recoil and is in phase with airflow.			
Reactance (X)	Energy generated by the recoil of the lungs after distention by a pressure wave out of phase with airflow			
Area of reactance (AX or XA)	Area under the curve between the reactance values for 5Hz and the resonance frequency			
Coefficient of variability (CV)	Statistical determinant of the trial-to-trial variability serving as an index of reproducibility			
Coherence	An estimate of the quality of impedance measurements. Provides an index of discrepancy between input and measured signals			
Compliance	An indicator of the ability of the lung tissue to distend in response to the pressure wave			
Frequency-independent change	When resistance values do not vary at different frequencies. If overall resistance is increased, this may be indicative of proximal obstruction.			
Frequency-dependent change	When resistance varies with frequency more than age-dependant normal values. This may be indicative of distal obstruction.			
Resonance frequency	The frequency at which the lung tissue moves from passive distention to active stretch in response to the force of the pressure wave signal; graphically when reactance is zero.			

Ann Allergy Asthma Immunol. 2011; 106(3): 191-199.





AOS - Plotting airway resistance and reactance against frequency



Healthy subjects:

- Rrs is almost independent of oscillation
- Rrs may increase slightly at higher frequencies due to the upper airways shunt effect (improper bracing of the cheeks)





Impedance

- "To Impede" \rightarrow Sum of all forces that oppose impulse generated
- Calculated from ratio of pressure and flow at each frequency (Zrs = P / Q)
- Zrs = Respiratory resistance (Rrs) + Respiratory reactance (Xrs)
- Rrs:
 - Energy required to propagate the pressure wave through the airways
 - Results are representative of airway caliber
- Xrs:
 - Amount of recoil generated against that pressure wave
 - Provides information about the mechanical properties of the respiratory system, particularly its capacitance and inertance





Respiratory resistance (Rrs)

- Includes central/proximal and peripheral/distal airways, lung tissue, and chest wall resistance
 - \circ R5 = Total resistance
 - \circ R20 = Central resistance
 - \circ R5-20 = Peripheral resistance







Respiratory resistance (Rrs)

- Includes central/proximal and peripheral/distal airways, lung tissue, and chest wall resistance
 - \circ R5 = Total resistance
 - \circ R20 = Central resistance
 - \circ R5-20 = Peripheral resistance
- Obstruction:
 - Rrs is increased
 - Site of airway obstruction is inferred from the pattern of Rrs, as a function of oscillation frequency
 - ✓ Central/proximal airway obstruction elevates Rrs evenly independent of oscillation frequency
 - ✓ In peripheral/distal airway obstruction, Rrs is highest at low frequencies and falls with increasing frequency (negative frequency-dependence of resistance (fdR))





Respiratory reactance (Xrs)

- Reactance (X) = Capacitance (C) + Inertance (I)
- "Capacitance":
 - > Measures the elastic recoil forces of the respiratory system
 - Reflects the compliance of the respiratory system
 - Primarily a property of the smaller airways
 - Reported as negative numbers
- "Inertance":
 - > Inertia is the tendency of a body to preserve its state of rest or uniform motion unless acted upon by an external force
 - ➢ Inertance refers to the resistance of the respiratory system to changes in airflow velocity
 - Primarily a property of the larger airways
 - Reported as positive numbers





Respiratory reactance (Xrs)

- Xrs is influenced by the oscillation frequency:
 - At <u>low frequency</u>, such as during normal breathing:
 - ✓ Capacitance dominates (i.e., compliance plays a significant role)
 - \checkmark When air enters the lungs, the lung tissue and airways expand, storing energy
 - ✓ This stored energy results in a negative reactance because it opposes changes in airflow, acting as a "spring" that pushes back against the movement of air.
 - At <u>high frequency</u>, such as during forced expiration or coughing:
 - $\checkmark\,$ Inertia of the air column in the larger airways dominates
 - \checkmark Inertia refers to the resistance of the air within the airways to changes in airflow direction or velocity
 - ✓ The larger airways have more mass and therefore have greater inertia. This inertia resists the changes in airflow and leads to a positive reactance.
- Reactance at 5 Hz (X5) is more negative in obstructive and restrictive lung diseases.







Resonant frequency (Fres)

- Frequency at which:
 - inertance = capacitance
 - total reactance = 0
- Separates low-frequency from high-frequency Xrs
- Fres is increased in both obstructive and restrictive lung diseases.







Reactance area (AX)

- Also known as the "Goldman Triangle"
- Area under the reactance curve from lowest frequency to Fres
- A quantitative index of total respiratory reactance (Xrs) at all frequencies between 5 Hz and Fres.
- Includes the total area dominated by the capacitance and reflects the elastic properties of the lung.
- As seen with reactance and Fres, Ax also increases in both obstructive and restrictive lung diseases.







Conditions	R5	R20	R5-R20	Х5	Ах	Fres
Peripheral obstruction	Increased	Normal	Increased	More negative	Increased	Increased
Central airway obstruction	Increased	Increased	Normal	Normal	Normal	Normal
Combined airway obstruction	More Increased	Increased	Increased	More negative	Increased	Increased
Restrictive lung disease	Normal / Increased	Normal	Normal / Increased	More negative	Increased	Increased













- Obstruction of the small, distal airways in the peripheral lung causes an increase in resistance (R) with a downward shift in reactance (X). In the presence of heterogeneity, R becomes curved.
- <u>Obstruction of the large, central airways</u> causes a parallel upward shift in resistance (R) while reactance (X) remains largely unchanged.

Ann Allergy Asthma Immunol 2011;106(3):191-199.





AOS bronchodilator responsiveness in asthma



Ann Allergy Asthma Immunol. 2017;118(6):664-671.





AOS and asthma severity

Except for central resistance, all parameters showed increased abnormality with increasing asthma severity.



Lung 2011;189(2):121-129.





AOS and asthma control

Odds ratio (95%CI) for asthma control over 2 years N=302; $FEV_1 = 97$ percent predicted; on LABA/ICS



Eur Respir J. 2014;44(5):1353-1355.





AOS in relation to type 2 inflammation

113 persistent asthmatics; FEV₁ 89%, ACQ 1.41; Mean ICS 644 microgram



Ann Allergy Asthma Immunol. 2018;121(5):631-632.











- COPD patients have a greater increase in peripheral airway resistance compared to asthma patients (greater increase in R5 (total resistance) *vs.* R20 (central resistance) and more elevated R5-20 (peripheral resistance)).
- Magnitude of changes in Fres, R5, R20, X5 and AX correlates well with COPD GOLD 1-4 severity.



Medicine (Baltimore). 2017 Nov; 96(46): e8543. Front Med (Lausanne). 2023; 10: 1181188.





AOS in the diagnosis of tracheobronchomalacia (TBM) in patients with severe asthma

- TBM is a comorbidity of asthma, worsening the prognosis and hampering an optimal clinical assessment.
- Prospective study of 33 (26 women) adult patients with severe asthma under biological treatment.
- TBM was diagnosed by bronchoscopy; considered significant when expiratory airway obstruction >80%.
- From the 33 patients included, 11 (33%) had chronic airway obstruction and 6 (18%) associated TBM.
- Significant differences were present in AOS values.
- AOS proves useful as a non-invasive tool to evaluate the presence and functional repercussion of TBM in patients with severe asthma.



<u>Delta Xrs</u>: Difference between reactance at 5 Hz in expiration and inspiration





Conference abstract, ERS 2023

Conclusions

• AOS is:

- A young but very promising technology
- An effort-independent rapid test
- A modem portable user-friendly device
- AOS measures:
 - $\circ~$ central/proximal and peripheral/distal airways, lung tissue, and chest wall resistance
 - o reactance
- AOS is useful to detect small airway disease in subjects with normal spirometry.
- AOS parameters are closely related to asthma control and T2 inflammation
- AOS should be used in conjunction with spirometry to fully characterize physiology and pathophysiology.





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Adding oscillometry to spirometry in guidelines better identifies uncontrolled asthma, future exacerbations, and potential targeted therapy

Stanley P. Galant, MD A ☑ • Tricia Morphew, MSc

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What about children?

Why perform PFTs in children?

- Children have a much greater prevalence of wheezing compared to adults.
 - 1 in 3 children wheeze at least once before the age of 3 years; about a third of those will continue to wheeze after age 6.



Taussig LM et al. JACI 2003; PMID 12704342. Martinez FD. NEJM 1995; PMID 7800004 Stein RT and Martinez FD. Paediatr Respir Rev 2004. PMID 15135126.

Why do PFTs in children?

- Respiratory illnesses (pneumonia, bronchiolitis, asthma) are the most common reason for hospital admissions in young children.
- Preventing recurrent exacerbations is a key goal of pediatric pulmonology.
- It is difficult to determine response to treatment without objective data, and preschool children are difficult to test with spirometry:
 - At BCH, 54% spirometry success rate in children 5 and under



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Oscillometry in pre-school children

- Associated with asthma symptoms in standardized questionnaires
- Predicts later spirometry abnormalities among children with asthma
 - AUC for R5 (>1.07) and Ax (3.92) = 0.75 (95% CI 0.6, 0.9)
- Feasible in preschool children, children with developmental delays, children with neuromuscular disease: success rates in preschool children ranging between 74-98%.





Chaya S et al. Front Pediatr 2022. PMID 35769219 Grell AV et al. Pediatr Pulmonol 2023. PMID 36704870

Oscillometry in pre-school children



Vyaire IOS https://intl.vyaire.com/products/ios-impulse-oscillometry



Thorasys Tremoflo C-100 Vielkind ML et al. Pediatr Res 2022. PMID 34326475

- Reference ranges: like in adults, lack of standardized prediction equations across all devices and ethnic groups
 - No GLI database exists for oscillometry; unclear effect of race/ethnicity



Height (cm)

Galant SP et al. Ann Allergy Asthma Immunol 2017. PMID 28583260 Chaya S. ERJ Open Res 2023. PMID 37057080

• Differences among platforms



Figure 1. Dot plots of Resistance (**A**,**B**,**C**) and Reactance (**D**,**E**,**F**) for Jaeger (IOS) (dots) and TremoFlo (stars) devices in the three clinical populations. $^{\Delta}p < 0.05$ for within group comparison of IOS and TremoFlo values.

Soares M et al. Sci Rep 2019. PMID 30765757.



• Differences among platforms



FIGURE 3 Impedance measurements in the mechanical test loads a) M1 and b) M6.

Dandurand RJ et al. ERJ Open Res 2019. PMID 31886158

- Below age 3, traditional oscillometry is difficult
- Options for lung function testing:
 - Tidal breathing analysis
 - Raised volume rapid
 thoracoabdominal compression
 - Multiple-breath gas washout
- Problems: specialized equipment, sedation, lack of normative values



Infant oscillometry

- Can perform oscillometry via a face mask in infants
- Our own work in Uganda: Pediatric Lungs in Uganda Study -2 (PLUS-2)
 - Measuring effect of air pollution and pneumonia on lung development in infants
 - 125 infants age 0 to 12 months with pneumonia + 100 healthy controls
 - Followed for 2 years with oscillometry every 3 months





* Staff member with her child pictured; used by permission





Challenges with infant oscillometry

- Software and hardware are still under development
- High variability due to
 - Short tests
 - Moving/non-cooperative infant
 - Lung/airway disease?
- No standardized QC/interpretation guidelines (i.e., reproducibility, acceptability)
- No reference values
- When to transition from infant to regular oscillometry

Developed interpretation guidelines

- Acceptability:
 - Review timecourse and reject measurements with obvious leak or artifact
 - Measurements should be at least 2 respiratory cycles
- Reproducibility:
 - Vt for acceptable measurements should be at least 70% of max Vt
 - Goal for R7 CV < 15%
- Process: each test independently read by at least 2 readers
- Results: Among all readers and for all parameters, correlation was > 0.90.



Preliminary infant oscillometry results: first 20 participants over 2 year period



	R7	р	R7-20	р	Ax	р
Age (per month)	-0.89 (-1.04, -0.74)	<0.001	-0.22 (-0.30, -0.14)	<0.001	-9.13 (-12.00, -6.25)	<0.001
Sex (M vs. F)	-0.64 (-6.43, 5.06)	0.83	0.14 (-2.35, 2.62)	0.92	-36.46 (-130.48, 57.57)	0.45
Weight (per kg)	-3.35 (-4.35, -2.36)	<0.001	-0.89 (-1.27, -0.51)	<0.001	-38.80 (-52.36, -25.24)	<0.001
Length (per cm)	-0.99 (-1.24, -0.73)	<0.001	-0.28 (-0.38, -0.18)	<0.001	-11.42 (-14.89, -7.95)	<0.001
Chest circumference (per cm)	-1.23 (-2.00, -0.45)	0.002	-0.28 (-0.58, 0.01)	0.06	-15.04 (-25.74, -4.34)	<0.001

Linear mixed effects model, with participant and reader as random effects

R7, R7-20, Ax by age



Age in months at follow up visit



Predicted probabilities with 95% CI from linear mixed effects model, with participant as random effect

Infant oscillometry



Klinger AP et al. Pediatr Res 2020. PMID 31935746.

Conclusions

- Oscillometry is a useful tool for measuring airway physiology in young children and infants.
- Like spirometry, it provides longitudinal data in the developing child and can be used to measure response to treatment.
- Infant oscillometry may identify signs of impaired lung development, early determinants of asthma, and markers of other respiratory diseases.



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