

Clinical Significance and Applications of Oscillometry – Supplementary Material

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Special Considerations Related to Interpreting Oscillometry

Useful physiological and pathological information from oscillometry can be obtained from the dependence of the frequency of oscillation. Most clinical oscillometric studies in children and adults have been conducted over relatively medium frequency ranges (between 4 to 50 Hz), although low frequency (less than 1 Hz) and high frequency (greater than 50 Hz) ranges have also been studied, particularly in infants. Much of the published literature has reported on whole-breath analysis to derive Z_{rs} , but there is increasing interest in “intra-breath” applications where a single frequency is used to track the breathing cycle temporally (1, 2). Additionally, the important effects of lung volume on oscillatory mechanics need to be better appreciated (3). R_{rs} has an inverse relationship with lung volume, particularly at low lung volumes where R_{rs} increases substantially. In children, this volume-dependence of R_{rs} is magnified in the presence of airway obstruction (4). The relationship between X_{rs} and lung volume is more complex, such that X_{rs} suddenly and abruptly decreases at low lung volumes due to airway closure (5-8). Such volume-dependent behaviours are best explained by parenchymal tethering of the airways, which allows lung inflation to increase airway calibre, or airway closure to occur during lung deflation. An understanding of these physiological relationships facilitates the clinical interpretation of

oscillometry measurements as the clinical relevance of this lung function modality continues to mature.

Oscillometry During Infancy

The vast majority of studies in infants have applied oscillations at raised lung volume during a period of apnoea, induced via the Herring-Bruer reflex. In infants, the equilibrium between tissue properties, lung volume, airway wall compliance, and airway diameter is highly complex and dynamically interacting (9). Consequently, oscillations outside of the medium frequency range have been applied to infants in an attempt to further understand the early origins of lung disease. For example, Zrs at low frequencies (below 1-2 Hz) contains information on both the resistive and elastic properties of the respiratory tissues (i.e., the parenchyma and chest wall) (10), as shown during methacholine challenge (11) and bronchodilator administration (12, 13) in wheezy and “healthy” infants. Similar low-frequency methods have been applied to a small number of preterm infants (14), but the clinical interpretation remains unclear.

High frequency oscillations (above 50Hz), which contains information on the airway wall properties, have also been applied to infants. These data reveal that the first anti-resonance (when the impedance is wholly due to resistance rather than reactive components which include elastic and inertial contributions) is altered in asymptomatic infants with wheezing disorders (15), consistent with changes in mechanical properties of the airway walls. Since both airway diameter and airway wall mechanics contribute to flow limitation (16) these findings support the notion that the mechanical properties of the airway walls may play a role in recurrently wheezing infants at baseline, as well as post-beta-agonist inhalation (17).

Most recently, oscillometry has been applied to infants during quiet sleep, utilizing medium frequency spectral analyses and the single frequency (intra-breath) method, with successful measurements obtained as early as the first day of life (18-20). This method has been applied to unsedated healthy infants at 6 weeks of age, to identify subjects at risk of developing severe respiratory illness in the first year of life, including those with lower respiratory tract illnesses and wheezing (21). Further studies in this emerging research area are likely to determine the broader role of oscillometry in detecting infants (and children) who may go on to develop chronic respiratory disease (22).

Effects of Lung Volume on Oscillatory Mechanics in Asthma

Van den Elshout and colleagues (23) have observed different responses of Zrs to changes in lung volume between healthy and asthmatic adults with and without bronchial hyperreactivity. Such findings suggest that oscillometry might be a useful adjunct for the diagnosis of bronchial hyperreactivity. The relationship between volume-dependent indexes and asthma control may also prove to be clinically useful, with earlier closure associated with worse control (24). The volume at which Xrs suddenly becomes more negative is higher in asthma, indicating earlier airway closure (5). Nilsen and colleagues (7) proposed a simple and easily performed technique using a slow vital capacity manoeuvre, in conjunction with Xrs measurements, to identify the critical volume resulting in apparent closure of airspaces (derecruitment) in asthma.

Derecruitment is the effective closure of airways to the oscillatory flow, which prevents transmission of flow beyond the occlusion and results in an apparent stiffening of the respiratory system, manifested as a more negative Xrs at low frequency. More recent work identified lung

derecruitment patterns (8) and relationship to closing volume as measured by single breath gas washout (25). Airway re-opening during large tidal manoeuvres is a modulator of airway obstruction in adult asthmatics (26). These mechanisms may be even more relevant in children, in whom FRC and airway closing volume have closer proximity.

Short and Long-Term Variability of Oscillometry in Asthma

Short-term variability (e.g., within-test or between-session on the same day) of oscillometry is greater than that seen with spirometry in children and adults (27, 28). As asthma is characterized by spontaneous variation in lung function over time (i.e., variable airflow obstruction), greater variability detected by oscillometry may have important clinical consequences. Que and colleagues showed greater variability of Zrs during a single 15 minute recording in adult asthmatics compared to healthy controls (29), and these findings have been replicated in some studies (30) but not others when log transformed (31). Veiga and colleagues (32) and Que and colleagues (29) demonstrated that this variability is proportional to airway obstruction. Gonem and colleagues (30), using a single 150-s recording of oscillometry, also reported higher Rrs and Rrs5-20 variability in asthmatics at Global Initiative for Asthma (GINA) (33) treatment steps 4 and 5, and with asthma exacerbation risk.

Longer time scale variation in lung function (i.e., over days or months) may also provide information on asthma control. Previous studies demonstrated that unsupervised home monitoring using oscillometry in adults yielded accurate and reproducible data (34-36), and that either the coefficient of variation or individualized standard deviations could be used to define day-to-day variability (28). In school-aged children, the variability of laboratory-measured Rrs

and Xrs over 5 days correlated with asthma control (37). More advanced methods may enable us to more adequately capture day-to-day variability of Rrs and Xrs obtained from home monitoring. Such analyses have predicted future deterioration in lung function, providing a potential measure of exacerbation risk (38, 39). Case studies provide promising evidence that home-based, parent-supervised, daily oscillometric measurements are predictive of future exacerbations in paediatric patients (40). Continuous, home-based monitoring with oscillometry to assess asthma control and to detect exacerbations is feasible and reliable in adults (39, 41). Greater day-to-day variability of Rrs and Xrs has been observed in mild-intermittent asthma versus health over days (28) as well as up to 6 months (42). The between-day variability of measurements is greater than that of FEV₁ (28, 43), which may reflect disease activity and the underlying physiological differences between oscillometry and spirometry (28, 43). These observations suggest a role for oscillometry as an objective and sensitive detector of asthma control and exacerbation, as well as a clinical indicator of exacerbation phenotype.

Upper Airway Shunt During Bronchial Challenge Testing

Upper airway shunting dampens any increase in Rrs during bronchial challenge testing, an effect that increases with greater lung impedance, such as in the presence of airway obstruction or in young children. This effect may be compensated for in part by using a “head generator”, or a different parameter derived from Zrs known as respiratory system admittance (Ars; the reciprocal of impedance i.e., $1/Zrs$) (44, 45). Ars represents the flow conductance of the total respiratory system, and corresponds closely to its predominating component, the bronchial conductance, especially when measured near resonant frequency.

Home Monitoring of Oscillometry in Patients with COPD

As with asthma, home monitoring of COPD patients with oscillometry is feasible (34, 43, 46, 47) and has been used to try to identify clinical deterioration in patients at risk of exacerbation (48). Although there was no difference in the overall risk of hospitalization compared to usual care, patients with a prior history of hospitalization and/or severe COPD benefitted from daily oscillometry monitoring linked to clinical intervention as lung function deterioration was detected. Whether the sensitivity and specificity of this approach can be improved by including symptomatic monitoring in this process remains to be tested.

The Use of Oscillometry in the Setting of CPAP for Obstructive Sleep Apnoea

In clinical settings of using oscillometry to monitor response to CPAP in OSA, oscillations should be applied through a nasal mask and tubing, with pressure and flow sensors not placed directly at the upper airway opening. Such technical modifications may require additional transducer calibrations and data corrections, as compared to conventional oscillometry delivered at the mouth in awake patients (49, 50). Interestingly, it has been shown that generation of oscillation signals for such application does not require an apparatus specific for OSA measurement, since a CPAP device can easily be modified to incorporate oscillometric measurements (51). Since appropriate application of oscillometry does not disturb sleep and does not modify upper airway tone (52), the technique has been incorporated into commercially available CPAP devices (53) to titrate the level of CPAP (54) either manually or as part of an automated control system (55).

Technical Aspects Related to Oscillometry in Mechanically Ventilated Patients

The measurement of impedance over lower frequencies encompassing typical ventilator rates usually requires interruption of artificial ventilatory support, although attempts have been made to estimate impedance from spectral analysis of standard volume-cycled waveforms (56, 57). Alternatively, various spectrally enhanced waveforms have been developed to allow for more robust and efficient measurement of low frequency impedance in ventilated patients (56, 58, 59). Some waveforms are even capable of maintaining gas exchange during the measurement (60, 61). If complete apnoea is required during measurement (to assess low frequency Zrs), the use of neuromuscular blockade may be considered in the patient who is appropriately sedated. Particular care must also be given to the instrumentation used for pressure and flow measurement at the airway, since it may easily become contaminated and non-functional due to secretions, especially mesh screen or capillary tube pneumotachographs (62). Should oscillometric measurements be acquired under varying concentrations of inspired oxygen or volatile anaesthetics, several calibrations of the flow sensor may be required to account for alterations in gas density or viscosity (63-65). The considerable nonlinear resistance of the endotracheal tube should be taken into account when measuring respiratory impedance in intubated patients (66-68).

Supplementary Table S1. Published reference values for Rrs and Zrs for healthy children and adults.

Author	Year	N	Ethnicity or Country	Age (yrs)	Oscillometry Device
<i>Children</i>					
<i>Preschool</i>					
Hellinckx (69)	1998	247	Cau	2-6	IOS
Malmberg(70)	2002	109	Cau	2-7	IOS
Shackleton(71)	2013	584	Mex	3-5	i2M
Er(72)	2019	151	Turkey	3-7	IOS
Duenas-Meza (73)	2019	96	Columbia	3-5	IOS
<i>Older Children</i>					
Frei (74)	2005	222	Cau	2-10	IOS
Ducharme (75)	2005	197	Cau	3-17	Custovit
Dencker (76)	2006	360	Cau	2-11	IOS
Amra (77)	2008	509	Iranian	5-19	IOS
Vu (78)	2008	175	Viet	6-11	Custom
Nowowiejska (79)	2008	626	Cau	3-18	IOS
Hagiwara (80)	2013	537	Jpn	6-15	IOS
Calogero (81)	2013	760	Cau	2-13	i2M
Gochiocoa-Rangel (82)	2015	283	Mex	2-15	IOS
Kanokporn (83)	2017	233	Thai	3-7	i2M
AlBlooshi	2018	291	UAE	4-12	tremoFlo
<i>Adults</i>					

Landser (84)	1982	407	Cau	-	Custom
Pasker (85)	1996	140	Cau	21-81	Custom
Guo (86)	2005	223	Cau	65-100	Oscilink
Shiota (87)	2005	299	Jpn	20-83	IOS
Brown (88)	2007	904	Cau	18-92	Custom
Newbury (89)	2008	125	Cau	25-74	IOS
Oostveen (90)	2013	368	Cau	18-84	multi*
Schulz (91)	2013	397	Cau	45-91	IOS
Abe (92)	2016	784	Jpn	46-90	MostGraph
Ribeiro (93)	2018	288	Braz	20-86	Custom
Moitra (94)	2020	191	India	18-88	IOS
De (95)	2020	253	India	18-81	IOS
Berger (96)	2021	439	Cau, Black, Asian, Hispanic	21-85	IOS

N:
number
of

participants; Cau: Caucasians; Mex: Mexicans; Jpn: Japanese; Viet: Vietnamese; UAE: United Arab Emirates. *: IOS, I2M, Oscilink, 2 Custom setups. IOS: Impulse Oscillometry System.

Supplementary Table S2. Threshold values for bronchodilator response derived from healthy children and adults.

Author/Year	Age (yrs)	N*	Drug (dose)	Oscillometry Index Cut-off
Helinckx 1998 (69)	3-7	228	Salbutamol (200 mcg)	Rrs5: -41%
Nielsen 2001 (97)	2-6	37	Terbutaline (500 mcg)	Rrs5: -29%, Xrs5: +42%
Malmberg 2002 (70)	2-7	89	Salbutamol (300 mcg)	Rrs5: -37%
Thamrin 2007 (98)	4-5	78	Salbutamol (600 mcg)	Rrs6: -42%, Xrs6: +61%
Oostveen 2010 (99)	4	144	Salbutamol (200 mcg)	Rrs4: -43%, AX: -81%
Shin YH 2012 (100)	2-6	29	Salbutamol (400 mcg)	Rrs 5: -19%, Xrs5:+24%
Calogero 2013 (81)	2-13	508	Salbutamol (200 mcg)	Rrs8: -32%, Xrs8: +65%, AX: -81%
Houghton 2004 (101)	adult	12	Salbutamol (800 mcg)	Rrs5: -16%, Xrs5: +27%
Houghton 2005 (102)	adult	12	Ipratropium (200 mcg)	Rrs5: -23%, Xrs5: +19%
Ostveen 2013 (90)	adult	368	Salbutamol (400 mcg)	Rrs5: -32%, Xrs: +44%, AX: -65%
Johansson 2021 (103)	adult	1495	Salbutamol (400 mcg)	Rrs5: -29%; Xrs5: +45%
Jetmalani 2021 (104)	adult	577	salbutamol (200 mcg)	Rrs6: -30%, -1.42 z-scores; Xrs6:0.57 cm H2O/L/s, 1.36 z-scores

* N: the number who received bronchodilator
 Bronchodilator response is defined as ((post-pre)/pre)*100.

Supplementary Table S3. Studies comparing cut-offs during bronchial challenge testing using oscillometry vs spirometry.

Author/Year	Population	Oscillometry device	Oscillometry index cut-off
<i>Paediatric studies</i>			
Lebecque 1987 (105)	17 children with AHR & 14 non-AHR	Oscillaire	50% increase R6 with histamine
Bouaziz 1996 (106)	38 asthmatic children	Pulmosfor 4-32Hz or 6 & 12Hz	70% change R12 and 1 hPa.s.L ⁻¹ decrease in X12 with methacholine
Jee 2010 (107)	50 asthmatic pre-school children & 41 children with cough	IOS	80% decrease in X5 with methacholine
Bailly 2011(108)	227 children with suspected asthma	IOS	50% decrease X5 with methacholine
Schulze 2012 (109)	48 children	IOS	45% increase in R5 or 0.69 kPa.s.L ⁻¹ decrease in X5 to methacholine
Jara-Gutierrez 2018. (110)	190 children	IOS	22% increase in R5, 41% decrease in X5, 82% increase in AX (for methacholine); for mannitol: 18% increase in R5, 21% decrease in X5, 40% increase in AX; for EVH: 23% increase in R5, 29% decrease in X5, 40% increase in AX
<i>Adult studies</i>			

van Noord 1989 (111)	53 adults	Custom device	47% increase in R5 detecting 15% decrease in FEV1 to histamine
J. Paireon 1994 (112)	119 adults with normal FEV1 from occupational screening.	Custom device	65% increase in R0 with methacholine
A.B. Bohadana 1999 (113)	71 adults with suspected asthma	Pulmosfor 4-32Hz	0.060 %rise R _{mean(4-32Hz)} /μg carbachol (DRS) or 0.066 %rise R10/ μg carbachol
M. McClean 2011 (114)	52 asthmatic and 15 healthy adults	Custom device	27% decrease in Grs6 or 0.93 cm H ₂ O.s.L ⁻¹ decrease in X6 with mannitol
Seccombe 2019. (115)	19 asthmatics and 10 controls	TremoFlo	27% increase in R5 and 47% decrease in X5 relative to 10% fall in FEV1 post-exercise

IOS – impulse oscillometry system; R0, R5, R6, R10, R12, X5, X12 – respiratory system resistance at a specified oscillation frequency.

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