Technical Standards for Oscillometry – Online Supplement

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Section E1. Estimation of impedance from flow and pressure raw data

There are several approaches for estimating Zrs from flow and pressure signals[1-5]. The most common one is based on the calculation of Zrs as the ratio between the estimated cross-spectrum between flow and pressure signals and the estimated auto-spectrum of the flow signal[6]. With this method, the entire recording of pressure and flow signals is divided into smaller data segments made of a predefined number of data points. Each segment is eventually multiplied by a function that varies from 0 at the beginning of the segment, increases to 1 in the center, and gets back to 0 at the end of the segment (a procedure called windowing). The estimation of Zrs spectra can then be obtained by averaging periodograms computed by using the Fast Fourier Transform (FFT) algorithm on each data segment.

Using this approach, the estimated impedance corresponds to the average value of the mechanical properties over the entire recording, implying the hidden assumption of stationarity of the mechanical properties of the respiratory system over this time. Impedance may change within a breath even in healthy subjects[7] but it may change markedly within a breath due to the presence of tidal expiratory flow limitation[8, 9]. There may also be large intra-tidal differences in Zrs between breaths because of fluctuations in end-expiratory lung volume[10] and/or breathing pattern[11]. Therefore, different approaches for data processing

and interpretation are required in presence of these conditions. The so-called "within-breath analysis" uses data processing algorithms able to estimate Zrs over very short time periods (i.e. over one or two oscillations), addresses this issue. This approach relies on forcing signals composed of fewer frequencies, which improves signal-to-noise ratio compared to signals with many frequency components, for the same total power of the signal[12]. In this case the impedance can be obtained from algorithms based on cross-correlation[11, 13], FFT [14, 15], or least squares[16] and their output is a time course of Rrs and Xrs over time (i.e. R(t) and X(t), respectively) for one[11] or more[17] frequencies.

It has been demonstrated that these mathematical approaches are theoretically equivalent and that the choice of the algorithm used per se, does not affect the results[13]. Alternatively, implementation of such algorithms in the computer software may lead to different results due to variations in numerical processing and round-off errors across different hardware platforms. Therefore, these algorithms require extensive validation to establish the accuracy of the estimated impedance regardless of the mathematical approach used. The results of validations should also be transparent and freely available.

E1.1 Derivation of mean impedance parameters

Once the Zrs is derived from the raw pressure and flow data, it may be reported as either spectra of Rrs and Xrs, or that of modulus and phase as functions of frequency, or as functions of time at each specified frequency when the within-breath approaches are used. Even if these data are reported graphically, it is necessary to report specific indices to quantitatively characterize the results of the test.

When the analysis is in the frequency domain (spectra), the values should include at least the values of Rrs and Xrs at a frequency representative of the low-frequency spectra (typically 4 to 6Hz), of mid-frequency spectra (typically between 8 to 12Hz) and of higher frequency spectra (typically 18-30 Hz or higher). Resonant frequency is identified by interpolating Xrs(f) from oscillation frequencies adjacent to the ones at which Xrs changes from negative to positive values. In some systems, the area under the Xrs(f) curve from the lowest frequency to Fres, termed AX[18], is also reported. This index increases with disease[19-28], and is attractive since it uses all the reactance data from the lowest frequency to resonance. However, a but a standardized approach for measurement (starting frequency, frequency resolution and numerical integration method) is still lacking. Also, in some children or in severely obstructed patients, Xrs(f) may not cross zero in the frequency range employed by the device, in which case AX cannot be measured since the values of Xrs at higher frequencies cannot be reliably extrapolated. The methods of AX derivation should be described in reports/publications.

E1.2 Derivation of Intra-breath impedance parameters

When within breath analysis is implemented, Rrs(t) and Xrs(t) can be divided into inspiratory and expiratory portions. Several parameters can be derived for both Rrs and Xrs, separately for inspiratory and expiratory phases of breathing. The parameters include the minimum, maximum, average, end-inspiratory and end-expiratory values of Rrs and of Xrs. Also, the differences between inspiratory and expiratory parameters have been described[8, 29, 30]. More recently, Rrs(t) and Xrs(t) were plotted against volume and against flow, and values such as the area of the Rrs or Xrs vs. volume loops were reported[9, 29, 31]. Intra-breath analysis therefore, allows measurement of the lung's dynamic behavior in relation to flow-dependence and volume-dependence. The rationale behind intra-breath analyses is that

airways diseases may affect Rrs and Xrs differently in inspiration and expiration, due to physiological asymmetry of lung mechanics. This asymmetry leads to phenomena happening during only specific breathing phases, such as expiratory flow limitation or airway closure. These differential mechanical responses during different parts of the respiratory cycle are exaggerated in disease due to for example, airway remodeling and alveolar dilation and destruction. More importantly, separation of Rrs and Xrs parameters into the inspiratory and expiratory phases potentially provides clinically useful information, over that of mean values, with potential for detailed characterization and phenotyping of airways and other lung diseases. This needs to be tested in clinical studies.

Different approaches for calculating impedance indices may result in different Rrs and Xrs values. To improve repeatability of results when the impedance is calculated over several breaths, a number of full breaths should be used i.e. data obtained from the start of inspiration to the end of expiration, instead of a constant time window, which could include partial tidal breaths[32]. This is because if the within-breath variations of Rrs and Xrs are large, inclusion of partial breaths at the start and end of the measurements may lead to variable results. For example, if the time window includes an extra inspiration in one test and an extra expiration in another, the number of inspiratory or expiratory segments within the recording will differ and may bias the results.

When within-breath approaches are used, manufacturers and users should specify the averaging process that is used. Averaging Rrs and Xrs data points from inspirations or expirations from all breaths is not equivalent to averaging data points from inspiration and expiration of each single breath and then averaging these for all breaths, as the duration of each breath is variable. Also, the different methods used to detect the beginning and the end

of a breath may lead to differences in results and therefore, the method used should be disclosed by manufacturers and users.

Tables

Table E1. Published reference values for Rrs and Zrs for children and adults.

Authors	year	n	ethnicity	age range (yrs)	setup
Children					
preschool					
Hellinckx [33]	1998	247	Cau	2-6	IOS
Malmberg [34]	2002	109	Cau	2-7	IOS
Shackleton [35]	2013	584	Mex	3-5	i2M
school					
Frei [36]	2005	222	Cau	2-10	IOS
Ducharme [37]	2005	197	Cau	3-17	Custovit
Dencker [38]	2006	360	Cau	2-11	IOS
Amra [39]	2008	509	Iranian	5-19	IOS
Vu [40]	2008	175	Viet	6-11	In-house
Nowowiejska [41]	2008	626	Cau	3-18	IOS
Hagiwara [42]	2013	537	Jpn	6-15	IOS
Calogero [43]	2013	760	Cau	2-13	I2M

Gochiocoa-Rangel [44]	2015	283	Mex	2-15	IOS
Kanokporn [45]	2017	233	Thai	3-7	i2M
AlBlooshi	2018	291	UAE	4-12	tremeFlo
Adults					
Landser [46]	1982	407	Cau	-	In-house
Pasker [47]	1996	140	Cau	21-81	In-house
Guo [48]	2005	223	Cau	65-100	Oscilink
Brown [49]	2007	904	Cau	18-92	In-house
Oostveen [50]	2013	368	Cau	18-84	multi*
Schulz [51]	2013	397	Cau	45-91	IOS
Ribeiro [52]	2018	288	Braz	20-86	In-house

n: number of participants; Cau: Caucasians; Mex: Mexicans; Jpn: Japanese; Viet: Vietnamese; UAE: United Arab Emarati. *: IOS, I2M, Oscilink, 2 home-build setups. IOS: Impulse Oscillometry System.

Table E2. Threshold values for bronchodilator response derived from healthy children.

Study	Age (yrs)	n*	Drug (dose)	Cut-off
Helinckx 1998 [33]	3-7	228	Salbutamol (200 μg)	Rrs5: -41%
Nielsen 2001 [53]	2-6	37	Terbutaline (500 μg)	Rrs5: -29%, Xrs5: +42%
Malmberg 2002 [34]	2-7	89	Salbutamol (300 μg)	Rrs5: -37%
Thamrin 2007 [54]	4-5	78	Salbutamol (600 μg)	Rrs6: -42%, Xrs6: +61%
Oostveen 2010 [55]	4	144	Salbutamol (200 μg)	Rrs4: -43%, AX: +81%
Calogero 2013 [43]	2-13	508	Salbutamol	Rrs6: -32%, Xrs8: +50%, AX: -

	(200 μg)	81%

* n: the number of children who received bronchodilator

Bronchodilator response is defined as ((post-pre)/pre)*100.

Table E3. Threshold values for bronchodilator response derived from healthy adults.

Study	n*	Drug (dose)	Cut-off
Houghton 2004 (salbutamol 800μg) [56]	12	Salbutamol (800 μg)	Rrs5: -16%, Xrs5: +27%
Houghton 2005 (ipratropium) [57]	12	Ipratropium (200 μg)	Rrs5: -23%, Xrs5: +19%
Oostveen 2013 [50]	368	Salbutamol (400 μg)	Rrs5: -32%, Xrs: +44%, AX: -65%

* n: the number of healthy adults who received bronchodilator

Bronchodilator response is defined as ((post-pre)/pre)*100.

Table E4. Studies comparing cut-offs during bronchial challenge testing using FOT vs spirometry.

Reference	**Population**	**FOT device**	**FOT cut-off**
Paediatric studies			
Lebecque 1987 [58]	17 children with AHR & 14 non-AHR	Oscillaire	50% increase R6 with histamine
Bouaziz 1996 [59]	38 asthmatic children	Pulmosfor 4-32Hz or 6 &	70% change R12 and 1 $hPa.s.L^{-1}$ decrease

		12Hz	in X12 with methacholine
Jee 2010 [60]	50 asthmatic pre-school children & 41 children with cough	IOS	80% decrease in X5 with methacholine
Bailly 2011[61]	227 children with suspected asthma	IOS	50% decrease X5 with methacholine
Schulze 2012 [62]	48 children	IOS	45% increase in R5 or 0.69 kPa.s.L^{-1} decrease in X5 to methacholine
Adult studies			
van Noord 1989 [63]	53 adults	Custom device	47% increase in R5 detecting 15% decrease in FEV1 to histamine
Hsuie 1993 [64]	141 adults (asthma, cough, psychogenic dyspnoea and healthy)	?	?
J. Pairon 1994 [65]	119 adults with normal FEV1 from occupational screening.	Custom device	65% increase in R0 with methacholine
A.B. Bohadana 1999 [66]	71 adults with suspected asthma	Pulmosfor 4-32Hz	0.060 %rise Rmean(4-32Hz)/μg carbachol (DRS) or 0.066 %rise R10/ μg carbachol
M. McClean 2011 [67]	52 asthmatic and 15 healthy adults	Custom device	27% decrease in Grs6 or 0.93 cm H_2O.s.L^{-1} decrease in X6 with mannitol

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

Figures

Figure E1. Oscillometry traces showing examples of artefacts caused by (A) obstruction of the mouthpiece by the tongue, (B) swallows and (C) mouth leaks due to the lips not sealing around the mouth piece. Obstructions cause obvious changes in flow, perhaps with accompanying changes in the volume-time curves during breathing. Changes in flow and volume-time curves when leaks occur may be more subtle and difficult to detect by visual inspection.

Figure E2. Prediction equations of Rrs (left panel) and Xrs (right panel) at 5 or 6 Hz as a function of height from studies of preschool-age to adolescent children. The shaded grey panel in the right panel are the upper and lower limits of normal values of Rrs5 and Xrs5 in young adults according to Oostveen et al [50].

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