Technical standards for respiratory oscillometry

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Early View

Task Force Report

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Technical Standards for Respiratory Oscillometry

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1. Overview of the document

There is increasing research on oscillometry, and increased interest and feasibility in its clinical application. Respiratory oscillometry measures the mechanical properties of the respiratory system (upper and intrathoracic airways, lung tissue and chest wall) during quiet tidal breathing, by the application of small pressure or flow oscillations (input or forcing signal) most commonly at the mouth.

Although the fundamental principles of oscillometry measurement are essentially the same for all devices, there are differences in hardware, data acquisition, and signal processing and analyses and breathing protocols that may lead to differences in impedance measurements. Furthermore, oscillometry is fundamentally a different measurement than traditional lung function measurements i.e. spirometry and lung volumes.

Oscillometry has been applied across a wide range of clinical and research settings, but these important topics will not be covered in this document. The aim of the present document is to highlight technical factors, both hardware, software and factors during patient testing, that potentially affect oscillometric measurements. Addressing these factors is critical for standardisation and obtaining accurate oscillometry measurements of the highest standards. Consequently, it is critical that all technical details of the hardware design, signal processing and analyses, and testing protocols are transparent and clearly reported to allow standardisation, comparison and replication of clinical and research studies.

This Taskforce Document contains general recommendations about oscillometric measurement including hardware, software, testing protocols and quality control. Given the wide range of scenarios in which oscillometry can be applied, many recommendations are general although some are more specific where appropriate. A summary of technical recommendations and clinical testing of oscillmetry are detailed in Table 1. The main differences of this update, compared with the 2003 ERS Taskforce document [1] are detailed in Table 2.

2. Introduction

Oscillometry (also known heretofore as the forced oscillation technique or 'FOT') was first described in 1956[2]. Usually, this technique is used to measure the mechanical properties of the respiratory system in a passive manner, i.e. manoeuvres such as forced expiration are not required. Oscillations can be superimposed over spontaneous tidal breathing or respiratory support ventilation and can be highly utilized in a number of clinical settings that routine clinical tests cannot, including in young children and during mechanical ventilation.

In oscillometry testing, a stimulus is applied to the respiratory system at the mouth. The input signal is either the pressure or flow oscillation, and the response (in terms of flow or pressure, respectively) is measured. The ratio of oscillatory pressure to oscillatory flow generated from this oscillatory stimulus is used to calculate input impedance, and represents the total mechanical properties of the respiratory system. The limitation of this representation of the respiratory system is that it is assumed to behave in a linear manner, whereas there is likely non-linear behaviour even in healthy lungs (primarily in the proximal and upper airways) and even more so in diseased lungs. Furthermore, ventilation is heterogeneous in healthy lungs and much more so in disease, which also affects this relationship. The most common and practical way to apply a forcing oscillation to the respiratory system is via the airway opening. Although there are other ways of applying a forcing oscillation to the respiratory system (for instance oscillating the chest wall[2]), this document will deal only with oscillometry where signals are applied at the airway opening as this is the most frequently encountered approach.

Pressure oscillations in the frequency range of 4 – 50 Hz, are commonly generated by a loudspeaker. Lower frequencies (i.e., < 4 Hz and as low as around 0.5 Hz) may be used, usually being generated by a piston type mechanical device[3] or pneumatic proportional solenoid valves[4], or loudspeaker. However, lower frequencies require the suspension of spontaneous breathing[5], which may be difficult or impossible in many patient populations. Hence, discussion of low frequency techniques will be minimal in this document. Excitation frequencies >35 Hz are easily produced by woofer speakers or by an interrupter valve[6], and may be used under certain conditions, to assess the acoustic or mechanical properties of the large airways and their walls. At present, such high frequencies are not commonly used in clinical settings, and will not be discussed further.

Although forced oscillations are simple in principle to administer, there are potential sources of error and variation which include variations in patient breathing, bacterial filters, artificial airways, device hardware and signal analysis, data processing and quality control strategies. A technical standards document was published in 2003[1]. Since then, there has been a large body of published research involving oscillometry in relation to improving the measurement technique as well as clinical studies, necessitating this update.

2.1 Key concepts of oscillatory mechanics of the respiratory system

Respiratory system impedance (Zrs) assesses the relationship between pressure and flow changes during oscillatory flow in and out of the lungs. Zrs has two basic components: resistance (Rrs) and reactance (Xrs):

$Zrs = Rrs + jXrs$ (j is $\sqrt{-1}$; the unit imaginary number).

The Xrs component of Zrs can be further defined as:

$Zrs = Rrs + j(\omega Irs - Ers/\omega)$ where Irs = respiratory system inertance and Ers = respiratory system elastance and $\omega = 2\pi f$ and f is the oscillation frequency.

Respiratory system resistance (Rrs) may be largely interpreted as airway calibre. Thus narrower and longer airways have higher resistances due to greater frictional pressure loss as air flows through them. Rrs is also affected by the heterogeneous distribution of resistances and reactances (see below) across the airway tree, where increasing heterogeneity increases the effective resistance at any given frequency[7]. There are also contributions from the parenchymal tissues and chest wall to the effective Rrs. Since Rrs reflects opposition to changes in flow, it is the component of Zrs which is in phase with flow and increased resistance will decrease flow for a given pressure input. It will not cause a 'time delay' (i.e. phase lag) in flow change, in relation to pressure change.

Respiratory system reactance (Xrs), in contrast to resistance, represents pressures changes that are out of phase with flow but in phase with volume changes. Therefore, Xrs has also been called the 'out of phase' component or the 'imaginary' component due to the nature of its mathematical description described above, involving'j', the unit imaginary number. The term 'imaginary part of impedance' is potentially confusing and is best avoided in clinical settings. Therefore, reactance is the preferred term for this component of Zrs.

Reactance is comprised of both inertance and elastance. Respiratory system elastance (Ers), which is 1/compliance, is a measure of the stiffness of the entire system (chest wall, lungs and airway walls) which, at commonly used oscillometry frequencies, includes compressibility of gas in the airways and alveoli. As volume changes, the resultant elastic forces cause pressure changes to *lag* behind flow changes ('time-delays' or phase lags) and hence elastance causes reactance to be negative. More negative reactance therefore indicates greater elastance or stiffness under oscillatory (dynamic) conditions (according to the Zrs equation above). Reactance is also affected by the heterogeneous distribution of airway calibres and lung compliances across the airway tree i.e. time constants (resistance x compliance)[8, 9]. This typically occurs in obstructive airways diseases. Heterogeneity (of time constants) makes the effective elastance (and hence Xrs) very sensitive to frequency (frequency-dependent). Increasing heterogeneity decreases the effective reactance (i.e. increases stiffness – elastance) at any given frequency.

Respiratory system Inertance (Irs) is an index of pressure losses mostly due to acceleration of the gas column in the central airways. Besides this airway component, which is determined by gas density and the ratio of airways length to surface area, Irs also has a lung - chest wall component, which is determined by the ratio of their respective masses to the squared surface area. In normal circumstances, the lung – chest wall component of Irs is small compared to the airway component. Irs becomes significant at higher frequencies where the bulk of gas and structures in the lung are oscillated at higher speeds. Inertance represents opposition to these accelerative forces, which act in the opposite direction (180^{o} out of phase) to elastance. Inertance therefore causes pressure to *lead* ahead of flow oscillations, and causes reactance to be positive.

When the respective magnitudes of inertance and elastance are equal, the elastic contribution exactly equals the inertive contribution. Being in opposite directions they cancel each other out and reactance becomes zero. This point is termed resonant frequency (Fres) and its corresponding frequency typically occurs in healthy adults at about 8-12Hz[10] and increases with decreasing age, where Fres can be >30Hz in young children. Hence when Xrs = 0, Zrs = Rrs. At frequencies above Fres, Xrs is positive in value because it is dominated by the apparent inertia of the gas and tissues.

Resistances, elastances and inertances of airways and subtending lung vary in magnitude, and are distributed in a variable manner within the lung i.e. there is inherent heterogeneity in the respiratory system. This heterogeneous distribution of Rrs and Ers properties in the lung explain an important mechanical characteristic of oscillometry; that of frequency dependence.

2.2 Frequency dependence

Respiratory system resistance (Rrs), elastance and inertance (hence reactance (Xrs)) vary with frequency, i.e. they are frequency dependent (see Figure 1). Heterogeneity across the airway tree, tissue viscoelasticity, the airway wall shunt and pendelluft, all contribute to frequency dependence. As frequencies decrease below 5Hz, Rrs increases rapidly while reactance becomes more negative as the mechanical properties of the lung (tissue viscoelasticity) and chest wall (elastance) dominate. As frequency increases within the commonly used frequency range (4-50 Hz), the lung and chest wall contributions diminish, and Rrs tends to be largely frequency-independent in healthy adults and is dominated by the airway properties. In healthy children, Rrs continues to show negative frequency dependence. As described above, with increasing frequency, the apparent elastance continues to decrease, i.e. Xrs becomes less negative, as inertia begins to dominate Xrs, i.e. positive frequency dependence.

In infants Zrs at a frequency < 1-2 Hz contains information on resistive and elastic properties of the tissue (lungs and chest wall)[11]. The contribution of the chest wall to Zrs decreases with increasing frequency and increases with increasing age[12]. Rrs is dominated by nasal resistance in infants because they are habitual nose breathers, and measurement therefore requires the use of facial mask[13]. The presence of heterogeneous ventilation due to airways disease may affect frequency dependence. At frequencies between 5-15 Hz, Zrs contains information on airway resistance, and at frequencies > 50 Hz, Zrs is dominated by acoustic properties of the central airways, as well as the mechanical properties of the airway walls[14, 15].

The negative frequency dependence of impedance may be conveniently represented as the difference between a high-frequency value of Rrs and a low-frequency value. However, the physiologic information depends on the frequencies that are used. At normal tidal breathing frequency and below, frequency dependence of impedance reflects mostly the viscoelastic properties of the respiratory system tissues in healthy lungs. In disease, frequency dependence over normal tidal breathing frequency and higher, is enhanced by the increased heterogeneity of Rrs and Ers due to increased variations in airway structure within a lung. Indeed, frequency dependence of Rrs in asymptomatic smokers with normal spirometry has been correlated with frequency dependence of compliance measured by esophageal manometry [16]. The shunting of applied flow oscillations into the upper airways (cheeks, pharynx, etc.) arises from increased glottic and subglottic airway impedance, can also increase overall frequency dependence of impedance[3, 17-21].

Modeling studies[19, 22] suggest that Rrs5 – Rrs20 may reflect the way in which the lung, behaving effectively as a single compartment (and with no involvement of tissue resistance), interacts with the upper airway structures into which flow oscillations are shunted. Hence, the physiological interpretation of frequency dependence remains uncertain, despite the common statement that parameters such as Rrs5-Rrs20 reflect small airway caliber. Unfortunately, there are as yet no published findings correlating pathology to frequency dependence. Therefore, this remains an area that requires further research.

2.3 Clinical settings in which oscillometry is applied

The oscillometry can be used in various clinical settings which include clinical lung function laboratories, field testing, home monitoring and intensive care. Oscillometry measurements have mostly been applied in airways diseases and paediatric lung diseases where oscillometry may have the most widespread clinical application. There are a number of available commercial devices, as well as local bespoke devices. Different devices or modifications of the hardware, oscillatory signals or data analysis methods may make them more suitable for different applications, e.g. testing children or in the intensive care unit.

Low frequency impedance (i.e., at frequencies encompassing typical breathing rates) can be measured in adults and infants, although this generally will require apnea and relaxation of the chest wall muscles[3, 5]. However, newer devices and signal processing techniques may allow measurement of low frequency Zrs during spontaneous breathing[23]. In infants, apnea can be induced using the Hering-Breuer reflex, by delivering positive airway pressure via face mask. Oscillometry can also be acquired during quiet sleep if apnoea is not required e.g., when single-frequency or higher frequency excitations are used. A wave tube technique is feasible as early as 1-3 days after birth[24-26].

Rrs, Xrs, Fres and other oscillometric indices provides data which complements 'traditional' measurements such as spirometry, lung volumes, specific conductance and diffusing capacity. Oscillometric measurements provide information in patients who are unable to perform spirometry e.g. poorly cooperative or frail. Oscillometry is an alternative to spirometry for conducting bronchial challenge testing in adults[9, 27-38]. It may be particularly useful in children given the difficulties with spirometry at young age[39-45] although there are additional technical issues to consider[46, 47].

Oscillometry has been applied to occupational health screening and large adult and paediatric population studies[25, 26, 48]. The short testing times and ease of administration for subjects are potential advantages in this setting. Oscillometry can be more sensitive than spirometry for detection of airways disease due to occupational exposure[48-55] but this area requires further research.

Self-administered, daily oscillometry made at home has been shown to be highly feasible in asthma and COPD patients[56, 57, 58]. The large amount of daily data allow analysis of day-to-day variability using sophisticated time-series techniques that may potentially be clinically useful for the diagnosis of asthma, monitoring its response to therapy and clinical phenotyping[59] . In a COPD study, early intervention triggered by worsening of oscillometric indices was not associated with any

differences in hospitalisation, or symptoms. However there was a significant reduction in repeat hospitalisations, leading to significantly reduced health care costs[60].

The use of oscillometry also has potential for optimising mechanical ventilation in the intensive care unit or operating room[61-63], although this is still an area of ongoing research. Impedance has been measured from spectrally enhanced, ventilation waveforms, of which some may allow uninterrupted ventilation[64-68] or by modification of the hardware of the ventilator, without having to add components.

3. Methods

This Task Force was initiated by its two co-chairs Gregory King and Ellie Oostveen, who developed the aims and outline of the document and brought together the members of the Task Force. All attempts were made to include representatives from key research groups who have been active in publishing research involving oscillometry. The Taskforce was initially a joint ATS/ERS project and subsequently an ERS project. The ATS withdrew support for the project at the end of 2018 due to slow progress.

The Task Force sought to produce a "state of the art" document bringing together the existing literature on oscillometry so that the evidence to guide device design, quality control and measurement are presented in an integrated, coherent manner. We also sought to identify areas of research needed to stimulate work and fill gaps in knowledge.

The Taskforce comprised 21 international members, identified from their profiles in the international research literature in oscillometry. The members were representative of a wide range of countries; Australia, Belgium, Brazil, Canada, France, Italy, Japan, The Netherlands, Spain and USA. There was representation from paediatric (GLH, EL, SJS, CD and EO) and adult (GGK, JB, JIB, PC, PLM, RLD, RF, II, CGI, DWK, DAK, JK, ENM, FM, BWO, CT, MvdB, EO) oscillometry researchers. Members included medical practitioners (GGK, KIB, PC, DWK, DAK, EL, BWO, MvdB). All members were experienced in the practical use of oscillometry.

All members provided signed declarations of Potential Conflicts of Interest which were managed according to the ATS and ERS rules and were updated regularly and at the conclusion of the project. No members were excluded because of potential and disclosed conflicts of interest.

The individual sections were initially outlined by GGK and EO and agreed to by the Taskforce at face-to-face meetings at the ATS and ERS congresses. The Sections were assigned to working groups that were organised by GGK and EO. The literature searches for each section were conducted by the Section authors, who used Pubmed, Google Scholar and Medline, limiting searches to English language publications but without limitation by year of publication.

The Section drafts were collated, checked and edited for stylistic consistency by GGK. All Sections were reviewed by all Taskforce members. Specific issues relating to content were discussed by email and at face-to-face meetings. The Taskforce met regularly between 2015 and 2018 at the ATS and ERS congresses, which were organised and chaired by GGK and EO, and were supported by both the ATS and ERS. Technical recommendations and standards of this document are a result of the Taskforce interpretation of the current literature including the previous ERS Technical Standards (2003) or other widely used and accepted reference values and technical documents. In case of conflicting conclusions technical recommendations and standards had to have the agreement of at least 18 of the 21 Taskforce members, including its Chairs

4. System design and testing

4.1 Input Signals

The physiological information contained in Zrs is strongly dependent on the frequency range over which it is measured. For example, in healthy adult humans, the viscoelastic properties of the lung and chest wall tissues have a major influence on Zrs below about 2 Hz. Conversely, the flow resistance of the airway tree and the mass of the gas contained within it become important determinants of Rrs and Xrs, respectively, above 2 Hz.. Therefore, the oscillatory frequencies used to measure Zrs must be appropriate to the physiological function that is being investigated.

When determining Zrs in spontaneously breathing humans, it is important to ensure that measurements of oscillatory pressure and flow are not significantly affected by unknown contributions from respiratory muscle activity. This can be achieved by having the lowest frequency in the applied oscillatory flow signal being greater than the frequency of breathing and its harmonics. The practical lower limit of frequency of the oscillatory signal in spontaneously breathing adults is thus typically 4-5 Hz[1, 69, 70], although this may vary depending on the breathing frequency. Even so, noise correlated with the breathing signal may still be present[71], as may occur with the high respiratory rates of infants and toddlers, or during tachypnoea in adults. There are, however, no data on the effect of respiratory rate on Rrs or Xrs in children. In adults, increased respiratory rates have been shown to increase Rrs and Xrs at 20 Hz in healthy and in symptomatic subjects with normal spirometry[72].

The best signal-to-noise ratio for Zrs measurements is obtained from a composite input signal consisting of the sum of discrete sinusoidal components with frequencies that provide good coverage over the entire frequency range of interest. Broadband waveforms may consist of small-amplitude random noise [73] or multiple sinusoids[71, 74]. Excitation waveforms consisting of frequencies that are mutually prime, such that none is an integer multiple of any other[67, 75], may be advantageous to minimize nonlinear distortions of impedance[76]. A convenient way to construct a mutually prime signal is to choose a desired fundamental frequency (e.g., 1 Hz) and then include frequencies that correspond to prime numbers above this fundamental (e.g. 2, 3, 5, 7… Hz) while not including the fundamental frequency itself i.e. 2-26 Hz pseudorandom signals. Some input signals are comprised of harmonics of a fundamental frequency such as, for example, in the Jaeger IOS (5Hz) and i2M (2Hz) devices. Harmonic distortion may occur with such waveforms if they induce large volume fluctuations in relation to the underlying breathing volume [64, 65, 76-78], especially when the respiratory system behaves in a substantially non-linear fashion i.e. in the presence of severe airflow obstruction or cyclic lung recruitment and derecruitment.

A comparison between oscillometry and IOS showed that Rrs measured by IOS was higher than by the 2-26 Hz pseudorandom signals, which was directly related to the magnitude of Rrs[79]. There were also subjectively similar differences between Rrs and frequency-dependence between 5 different devices in healthy subjects, although these differences could have been due to differences between populations between centres[10].

The size of the sinusoidal components in a composite oscillatory signal should be such that there is sufficient signal-to-noise ratio at each frequency. The peak-to-peak excursion should be ≤0.3 kPa. A convenient example is to have equal power at each frequency[77] in the flow signal. The phases of the sinusoidal components should be chosen to minimize the peak-to-peak amplitude of the oscillatory signal, again to minimize the influence of nonlinear behavior in the lung[74]. Details of signal composition, including signal-to-noise ratio, for all oscillometry devices should be publicly available.

4.2 Technical recommendations and standards for manufacturers:

4.2.1 Calibration

Although a variety of configurations have been used[69], Zrs is most commonly measured from the signals of two sensors placed at the mouthpiece level: a pressure transducer and a flowmeter based on a pneumotachograh with a differential pressure transducer. Sensor calibration ensures adequate corrections to compensate for inadequate device performance[80]. Firstly, on the assumption that a sensor is linear, static calibration should ensure correct gain and zero offset (taking into account possible temperature and position drifts). Secondly, dynamic calibration should compensate for a sensor's frequency response by digitally compensating Zrs for the measured dynamic responses of the pressure and flow transducers or other instrumentation[81]. Dynamic calibration must ensure that the sensor signals are unaffected by mechanical vibrations at the desired oscillation frequencies. The common-mode rejection ratio (CMRR) of the pressure transducer attached to the pneumotachograph should be sufficiently high to minimize potential errors[82]. Alternatively, dynamic calibration procedures are available to compensate for both instrumentation frequency response and CMRR during oscillometric measurements[83]. As the dynamic response mainly depends on the physical dimensions of sensors and tubing[84], their frequency response usually does not change over time. Therefore dynamic calibrations, in contrast to static calibrations of gain and zero offset, are not periodically required.

4.2.2 Test load

Achieving accurate measurements of Zrs depends on many subtle details in the utilised hardware (sensors) and software (data processing). Procedures for characterizing and calibrating for sensors responses are well defined, and if followed correctly should not result in significant errors in Zrs measurements. By contrast, there is no unique data processing procedure (e.g. filtering, averaging, frequency analysis, data rejection criteria) that is ideal. Furthermore, there are many suitable numerical algorithms to implement these procedures. Manufacturers must provide documentation on the accuracy of their devices for measuring resistances and reactances of a static test load. The magnitude of that load impedance should be above the absolute value of Zrs that is expected for any given patient or subject population in which the oscillometric device is to be used, including impedances encountered in children and adults during bronchial challenge testing. Therefore, it is recommended that test loads for adult testing be approximately 15 $hPa.s.L^{-1}$ and for children around 40 $hPa.s.L^{-1}$.Test loads of insufficient impedance may potentially lead to errors in measurement[85]. This test load should be supplied to the end-user for daily verification. At present, most test loads

consist solely of a mechanically resistive component. Ideally, test loads should also include the elastic and inertial components of impedance.

Testing and comparing how different specific oscillometric devices behave in practice requires something more than ensuring that they meet general recommendations and how they measure static loads. Ideally, robust and accurate Zrs measurements should require a patient simulator with well-controlled (but variable) mechanical properties, breathing patterns and artefacts[86]. Devices that simulate human physiology are common in medical device testing, especially for respiratory and gas flow measurements. For example, the ATS-ERS provide very specific recommendations for performance testing of spirometric devices, using devices that simulate high-fidelity flows typical of forced expiratory manoeuvres[87]. There are equivalent albeit less specific recommendations, for evaluating automatic CPAP devices[88] and mechanical ventilators[89], where using a well-characterized patient simulator as a reference is required. It is therefore equally important that such a test load be developed for objective assessment and comparison of oscillometry devices under realistic conditions.

4.3 Verification by end-users

End-users of commercial devices perform verification with impedance test loads and not calibration. Thus the following recommendations pertain to verification. Like other lung function equipment, verification with test loads should be performed daily or each day that the instrument is used, particularly if being used for clinical testing, as would be common practice for other lung function equipment in the pulmonary function laboratory[90]. More frequent verification may be needed during field testing when environmental conditions may change. Research papers should report how often device verifications occur, the mechanical characteristics of the load(s) verified, and the accepted tolerance of the verification. The recommended tolerance for the verification is ≤ ±10% or ±0.1hPa.s.L^{-1}, whichever is met first. If volume changes are to be measured in patients, then the accuracy of volume measurements should be verified against a calibration syringe and comply with ATS standards[87].

4.4 System resistance and dead space

The oscillometric system and the additional bacterial filter can add dead space and additional resistance to breathing. It is important to compensate for the bacterial filter resistance and combined dead space of filters and connectors for measurement accuracy and advisable to maintain low overall oscillometric system resistance and dead space to minimize potential effects on breathing pattern which can increase tidal volume depending on measurement duration. The oscillometric system without a bacterial filter in place should have a resistance of <1 hPa.s.L^{-1} at 5Hz or less. There are numerous bacterial filters available for use with oscillometric systems, which will have a range of resistances. A single study showed differences in impedance measured with different filters by IOS in healthy adults[91]. A single study using the interrupter method in asthmatic children aged 4-16 years, found a mean increase of 1.2 hPa.s.L^{-1} but there was a wide variance of ±3.4 hPa.s.L^{-1}[92]. General recommendations are to use low resistance filters of <1 hPa/L/s at 5Hz or less, to regularly measure the resistances of the filters and to compensate for the combined

resistances of the oscillometric system + filter. The total equipment resistance of an oscillometric system should thus be <2 hPa.s.L^{-1} at 5Hz or less.

The recommended dead space for oscillometric devices used for testing adults is the same as for lung volume testing[90]; <100ml inclusive of the bacterial filter. Due to the mixing caused by the oscillatory flow, the effective dead space can be less than the physical volume. In pre-school children, it should be <70ml inclusive of the bacterial filter[93].

5. Signal Processing for Oscillometry

Processing for oscillometric signals has major impacts on the overall accuracy of oscillometry measurements. Signal processing, either analog, digital or a combination of the two, addresses five main tasks: 1) estimation of respiratory system impedance (Zrs) from raw flow and pressure data; 2) filtering to reduce the noise that is always present in the signals; 3) compensation for the frequency response characteristics of the sensors and other components; 4) accounting for instrument dead space, 5) derivation of impedance parameters and 6) calculation of indices for quality control of the measurements.

A description of signal analysis methods used in oscillometry to derive impedance parameters appears in the on-line supplement.

In summary, in modern oscillometric devices, signal processing constitutes a critical component that has major effects on the performances of the overall system. Given the variety and the complexity of the algorithms used, manufacturers should make the information listed in Table 4, available to the users, either by reporting them in research publications or making them available on request. Also, manufacturers are responsible for extensive validation of oscillometric devices in a variety of conditions, including simulations of both healthy and diseased conditions, and to disclose the validation set-ups and procedures and the values of test loads used.

6. Testing Protocols and Procedures

Unlike spirometry, oscillometry can be acquired using varying protocols and under varying breathing conditions, depending on the mechanical properties of interest. Oscillometric measurements are most commonly made during resting tidal breathing but have also been made during larger volume excursions e.g. from FRC to TLC or TLC to RV[94-96]. Like spirometry, oscillometry is also potentially affected by upper airway artefact, in the form of swallows, vocal cord closures, coughs, incorrect positioning of the tongue and mouth leaks (see Figure E1).

For all oscillometric acquisitions, patients should be breathing in a relaxed and stable manner, seated in upright posture with correct head position, cheek support, mouthpiece seal and tongue position. Therefore, careful instructions should be provided so that during the acquisition, patients breathe with the same tidal volumes and frequencies as during stable, relaxed conditions. Prior to the measurement, a quick visual check for leaks around the mouth and use of a nose clip is essential, as well as ensuring that a stable period of tidal breathing is achieved. Table 5 lists the minimum instructions and information that should be provided to the patients prior to testing.

Adequate training of clinical staff and/or researchers administering the oscillometry test is required, given the potential for artefacts to affect the final results. This is particularly important in children.

Oscillometry testing protocols will vary according to the many applications that oscillometry is suited for, e.g. infants, preschool and school-aged children, elderly, epidemiological studies, occupational screening, home-monitoring. There are however, general principles on which an oscillometry acquisition protocol should be based and these are listed immediately below.

6.1 Minimum number of technically acceptable replicate measurements

The number of technically acceptable measurements used to determine a mean value will affect the variability of the test. Recent work in adults suggests that 2 technically acceptable measurements result in the same mean resistance and reactance values as 3 or more replicate measurements, regardless of measurement duration[97]. There is no comparable information of the effect of the number of replicates in children. However, it is recommended to use at least 3 replicates, which are deemed acceptable after application of specified quality criteria: visual inspection, within-session coefficient of variability (CoV) and automated signal processing. The replicates that are used to derive the indices should all be completely free of artefacts. Note that in some applications, artefacts may be removed prior to calculations of mean indices (see section 8; Quality Control).

It is recommended that the 3 replicates used to derive indices should have a CoV of Rrs, at the lowest oscillation frequency, of ≤10% in adults and ≤15% in children, although there are currently no published data to support these cut-offs. Use of an arbitrary CoV to select replicates to calculate indices will force the selection of values that are close to each other, and will exclude outlying values. Use of CoV and its specified threshold value to select replicates, should be declared in the report or methods of publications.

While multiple replicate measurements remains the norm in laboratory testing, longer recording durations with a single measurement may be more practical and feasible in field testing or unsupervised home monitoring due to practicality and feasibility[56, 58].

6.2 Duration of acquisition

The length of acquisition during infancy will depend on the method used. For example, low frequency oscillometry is measured during an apnea (via the Herring-Breuer reflex) and therefore should not exceed a reasonable breath-hold time period (typically 5 to 8 seconds). However, in quietly breathing sleeping infants, there is no reason why the suggested 30 or 60 second collection time (to maximise the number or respiratory cycles) could not be also considered in this population.

In school aged children, data acquisitions of 60 seconds resulted in better within-session and between day reproducibility than 30s, 16s or 8s acquisitions[98]. Longer acquisitions are likely to be more challenging in younger paediatric populations. In healthy adults and adults with asthma or COPD, within-session variability also decreased as acquisition duration increased from 16s, 30s and 60s[97]. Additionally, there were small but statistically significant differences in mean Rrs or Xrs, between triplicate measurements of 16s, 30s and 60s, in healthy adults or those with asthma or COPD[97].

A suggested minimum acquisition time that would be suitable for high-school aged children and adults is 30 seconds and for children <12 years of age is 16 seconds. This would allow recording of at least 3 artefact free breaths, but be short enough to be practical and to avoid movement or fatigue. There are however, a range of acquisition times that have been used, which has been dependent on the clinical application and the populations studied, e.g. infants and toddlers vs adults; research studies versus clinical measurements; and the severity of the disease. The wide range of testing situations arising from the combinations of patient, disease and laboratory conditions implies that the duration of oscillometry acquisition will vary to suit the population being tested, with the goal of achieving reproducible measurements as described above. As such, the testing durations used should be stated in the laboratory report or research publication to allow replication and comparison of results.

6.3 Effect of volume history

Volume history potentially affects impedance measurements in individuals with airways disease[99-101] and also in healthy subjects during bronchial challenge testing[102]. Deep inspirations have variable effects on lung function that differs between diseases[99-101, 103-106].

Deep breaths (i.e. inflation to TLC) during testing potentially affect results in asthmatics because of the known bronchodilator effects of deep breaths in asthma[107-109]. Thus, standardisation of lung volume history is necessary. The response to deep breaths during bronchial challenge tests also differs between asthmatics and non-asthmatics[99-101]. In non-asthmatic subjects, deep breaths prior to inhalation of an airway smooth muscle agonist protect against airway narrowing, while deep breaths after inhalation leads to sustained airway dilation. In asthmatic subjects, deep breaths may have reduced but variable effects in protecting against airway narrowing or dilating airways post-bronchoconstriction, depending on disease state or severity[99-101]. Indeed, deep breaths can even worsen baseline airway obstruction, measured by either spirometry[110] or oscillometry[111]. Therefore, bronchial challenge using oscillometry may be more sensitive for detecting airway hyperresponsiveness, particularly when it is mild. Since oscillometry is measured during tidal

breathing and without deep inspirations, the sensitivity of such tests may differ compared with tests using spirometry. However, further studies on this are needed.

Until the effects of volume history on oscillometry parameters and bronchial challenges are better characterised, oscillometric testing is recommended before tests requiring deep breaths (exhaled nitric oxide, spirometry, diffusing capacity), as well as allowing a standardised length of time during which deep breaths are withheld before performing oscillometry. The order of testing and duration of withholding of deep inspirations should be standardised locally and documented in reports and publications.

7. Quality control: criteria for test acceptability

The exclusion of artefacts occurring during the test (cough, glottis closure, leaks, etc.) critically impacts on the accuracy of impedance measurements. This will require a quality control processes that identify common artefacts such as leaks, swallows, coughs, incorrect tongue placement. Real-time display of volume, flow and pressure traces allows the operator to identify the presence of artefacts (see Online supplement Figure E1)[71, 74] , which in most situations requires repeating acquisitions until at least three measurements have been recorded that are free of artefact.

7.1 Identification of artefacts

Subjective quality control criteria include ensuring that the tidal volumes and rate during acquisition should be stable and, that there are no pauses in volume signal accompanied by zero flow, sudden changes or spikes in resistance and pressure, which may represent swallowing, breath holds, glottic closures and mouth leaks (see Online supplement Figure E1)[98]. A protocol with criteria for test acceptability by visual inspection should be developed for any laboratory or project, and be freely available, to ensure capture of sufficient, artefact-free replicates as stipulated in the protocol. Differing acceptability criteria for consistency of tidal rate and volume may affect mean Rrs and Xrs values, and their repeatability, particularly in disease[112] where Rrs and Xrs may be highly flow dependent. Study of the effects of varying acceptability criteria on impedance values are needed.

Windows containing negative resistances should be excluded as they are physiologically implausible. They may result from poor design of hardware or signal processing, or noise artefacts such as cough[113]. Leaks manifest as sudden large decreases in $|Zrs|$, although the changes in flow-time and volume-time traces may at times, be subtle. Swallowing or transient airway occlusion manifest as large values of impedance at zero flow[98, 114]. Artefact removal can be based on statistical filtering of impedance values from individual windows[20, 115] or on the basis of complete breaths[98]. The latter reflects interest in within-breath indices[116], and results in lower test variability.

Automated strategies for removing artefacts, particularly when within-breath parameters are derived, are still a topical area of research. These include use of parameters such as the flow shape index, which represents how the shape of the time course of the oscillatory flow approximates the theoretical one[117] or other criteria[113, 118]. Laboratories and research studies may exclude individual breaths, only the affected segments, or entire recordings. Such exclusions should be reported or made readily available, as well as the exclusion criteria used.

7.2 Use of coherence

Originally, when the cross-spectra method for calculating Zrs was used, the coherence (γ^2) between flow and pressure at each frequency was commonly used to determine whether a measurement contained too many artefacts, and thus should be discarded. Coherence can be interpreted as a causality index between the input (flow) to the respiratory system and its 'linearly' -dependent output (pressure)[119], or vice versa. Coherence values range between 0 (no causality at all) and 1 (perfect causality) but values less than 0.90 or 0.95 were typically discarded[3, 21, 120, 121], as low coherence values can result from various processes such as poor signal-to-noise ratio, non-

linearities, cardiogenic oscillations, or band-overlap between the excitation and spontaneous breathing waveforms. However, there are potential problems with using coherence in this mnner, including: 1) varied approaches used by manufacturers to calculate its value; 2) for single-frequency tracking of impedance over time, coherence is dependent on windowing[122]; 3) coherence is often reduced in disease[36] such that an arbitrary cutoff would bias results; and 4) high coherence values do not ensure the absence of artefacts or measurement errors. While low coherence is generally indicative of noise or artefact, because of the differences between devices and between different diseases, coherence is no longer recommended as criterion for quality control.

7.3 Use of biological controls

Use of biological controls should be standard practice in research and clinical laboratories. A biological control is a healthy non-smoking subject, e.g. a lung function scientist. First, sufficient Zrs data (e.g. at least 10 separate measurements) should be obtained in a relatively short time-interval (e.g. a few weeks) so that the average and confidence intervals of Zrs are known. If a subsequent measurement is outside the confidence interval, the oscillometric system should be carefully evaluated. Manufacturers are encouraged to develop automated quality-control software to assist and enhance the utility of the biological control. The weekly use of a biological control subject is recommended for oscillometry equipment that is used on a regular basis.

8. Reporting of results

8.1 Reporting of measurement details:

Details of the hardware and testing procedures should be reported to allow comparison and replication (see Table 6). For scientific publications, this will require an online supplement in many journals given the significant volume of detail that should be reported.

8.2 Reporting acceptability and repeatability criteria

It is important to report the number (or range) of individual recordings that are used to calculate impedance, after the rejection criteria and quality control are met. This will allow comparison and reproduction of results between laboratories. The CoV should also be included in the report and if the CoV is higher than the specified upper limit, the results should be flagged so that this is taken into account and the results may be interpreted with caution. Manufacturers must make these features available in real-time to ensure that adequate data can be collected in a testing session. The laboratory quality control processes should be documented and included in research publications (see Table 6). Currently, there is little information on which oscillometric parameters should be included in a basic report. Such parameters should be determined by the users and manufacturers should allow flexibility in report design. However, testing protocols, quality control criteria and verification procedures should be reported. Hence Figure 2 is an illustrative example only, of what might be included in a report. Note that this is not a recommended reporting template. The 'Technical Notes' might be made available in the Laboratory resources, rather than appear on the laboratory report.

8.3 Reference values

There are numerous published values in different populations, for children and adults[123] (see Table E1 in the Online Supplement). As with all lung function tests, the appropriateness of any predicted equations for a particular oscillometric device, should be determined for the population in which it is to be applied by each laboratory. There is a need to obtain normative values, including bronchodilator responses, for children and adults from different countries using standardise breathing protocols and signal analyses, from which multi-ethnic normative values similar to the GLI values for spirometry[124] may be derived. The possible differences in measurements between devices[10, 79, 125-127] also requires further study. In the absence of this data, reference values derived from a device that is most similar to the device being used is recommended. It is also recommended that Z-scores for each parameter be included in the output, where the necessary statistical data are available. This avoids the problem of having a predicted value close to zero, when use of percent predicted can become very large and problematic in terms of clinical interpretation.

8.3.1 Children

Standing height is the dominant predictor of Rrs[128], although sex is also an independent predictor in one report[129] but not in others of preschool and school aged children[130, 131]. Most normative studies on Rrs in preschool children have observed no significant effect of weight or age on Rrs. In adolescents, sex-related differences in Rrs have observed, but were small with predicted Rrs for girls being < 5% larger than that for boys[129, 132, 133]. Except for one study[134], Xrs in preschool children was described as a linear function of height (see Figure E2, left panel)[128, 134]; and both height and sex[129]. There is a large scatter in the prediction of Rrs and Xrs at low frequency in young children and therefore, the appropriate predicted equation for any given pediatric population should be determined for that population. In the absence of local regional or geographic data, use of the reference equations from studies in which the devices and population most closely approximate the local situation is recommended.

8.3.2 Adults

Older studies were undertaken with equipment no longer on the market and few published studies were conducted with currently available commercial devices. The most comprehensive and recent study involves multiple centres and multiple, currently available oscillometric devices[10].

9. Bronchodilator and bronchoconstrictor responses

9.1 Bronchodilator responses

Whenever possible, baseline data should be expressed as Z-scores since raw values are dependent on height and age. The dose of salbutamol used to assess bronchodilation should also be reported. It is still debatable whether the bronchodilator response should be expressed as relative or absolute change[135, 136]. In children and adults, the absolute change in Rrs and Xrs is dependent on the baseline value[137] but the separation using absolute values is greater between subjects with disease and control subjects[138], compared to when relative values are used. Therefore, a Z-score postBD change has also been proposed[139], which would overcome these problems. This would require the bronchodilator responses in a healthy population to be determined, from which an upper 95^{th} percentile could be determined for each relevant oscillometry parameter. The distribution of responses may not be normal and arithmetic transformations, e.g. log-transformation of the ratio of postBD to preBD values[140], may normalize the data.

Rrs and Xrs are both volume dependent[95, 141]. Since bronchodilatation reduces lung hyperinflation, this would also potentially increase Rrs and decrease Xrs, which would be in opposite directions to the direct effects of bronchodilator on airway caliber and airway closure. The interpretation of bronchodilator responses of Rrs and Xrs therefore, may not be straightforward and could cause some disparity with spirometry response.

Table E2 in the Online Supplement shows the published papers on bronchodilator responses in healthy children, which were chosen based on the presence of the 95th percentiles for the responses, which allowed determination of a threshold value. The thresholds for bronchodilator responsiveness are remarkably similar, which for Rrs is around -40% in preschool-aged children at 4-6 Hz forcing frequency, and for Xrs being between 40 – 60% and -80% for AX. In older children, the threshold may be slightly lower for Rrs at around -35% but similar for Xrs and AX being 40% and -80%, respectively. Therefore, it is recommended that the thresholds for defining a positive bronchodilator response, for both adults and children, are -40% decrease in Rrs5, +50% increase in Xrs5 and -80% decrease in AX.

Table E3 in the Online Supplement shows the published papers on bronchodilator responses in healthy adults. There are only 3 published papers in healthy adults, with only 1 paper with sufficient numbers to provide confident thresholds[135]. Therefore, the thresholds from this paper could be used to define bronchodilator responsiveness thresholds but the limitations of this should be recognised. More studies of bronchodilator responsiveness in healthy children and adults are therefore required, both to provide better validation, comparison between populations and between devices, and to allow definition of thresholds based on Z-scores.

9.2 Bronchial challenge testing

Oscillometry is an alternative to spirometry for conducting bronchial challenge testing in adults[9, 27-38] and children[39-45]. However, particularly in children there may be underestimation of the change in Rrs during challenge testing due to upper airway artefact and wall shunting[46]. This effect may be reduced by using admittance (1/Zrs) instead of Rrs[47, 142].

So-called cut-offs for oscillometry during bronchial challenge testing have been determined in older children and adults, by referencing the standard cut-offs from spirometry (see Table E4 in the Online Supplement). However, potentially better cut-offs to define normality could be derived from studies of general populations samples, without reference to spirometry gold standards. Such cut-offs could have better clinical utility than spirometry based tests. Airway hyperresponsiveness measured by oscillometry is reproducible[28, 30, 41, 143] and is correlated with responsiveness measured by FEV1.

The sensitivity and specificity of suggested cut-offs for a positive challenge test using Rrs, Xrs, Grs and dose response slopes, for a number of different forcing frequencies, can be calculated for the published studies (see Table E4). There is a wide variability across studies, which may be explained by differences in methods used and differences in study populations. It is unlikely that differences in measurements between different devices significantly affect the measurements of airway hyperresponsiveness, but direct comparisons (i.e. replicate challenges with different oscillometry devices) have not been made. Given the variability discussed above, it is currently recommended that local thresholds should be developed which would be appropriate for the specific population with a specific device.

There is some discordance in detectring airway hyperresponsiveness between bronchial challenges done with oscillometry versus with challenges done with spirometry, in which case changes in oscillometry indices may provide additional information to spirometry. For example, some subjects

report symptoms during the challenge test without accompanying changes in FEV1 but have changes in Rrs and AX, which suggests airway narrowing and closure [144, 145]. This disparity between spirometry and impedance changes are likely related to differences in volume history (see Section 6.3 Volume History). In obese asthmatic and non-asthmatic individuals, bronchial challenge is associated with greater expiratory flow limitation measured by Xrs. This measurement was shown to correlate better with symptoms than did FEV1[146].

10. Future research to improve the technical performance of oscillometry

More research on quality control methods for oscillometric parameters and their effects on repeatability, across various age ranges and in different respiratory diseases and clinical settings e.g. the intensive care setting and population screening; will further improve the quality and standardisation of measurements. This may include studies of tidal volume and rate, automated detection of artefacts, effects of CoV cut-offs and effects of gas mixtures and ventilation hardware in the ICU. Large studies to determine multi-ethnic population normal values, equivalent to the Global Lung Initiative values for spirometry[124], are needed. Dynamic impedance, similar to the waveforms used for spirometry validation, should be developed and could be used to standardise oscillometry devices.

Improving the performance standards of oscillometry devices, standardising and improving the way in which it is administered, and improving the quality control of the final measurements, will increase the overall quality of impedance measurements in the clinical and research settings. Hence, the authors are of the strong belief that this will allow the benefits of oscillometry in medicine to be realised.

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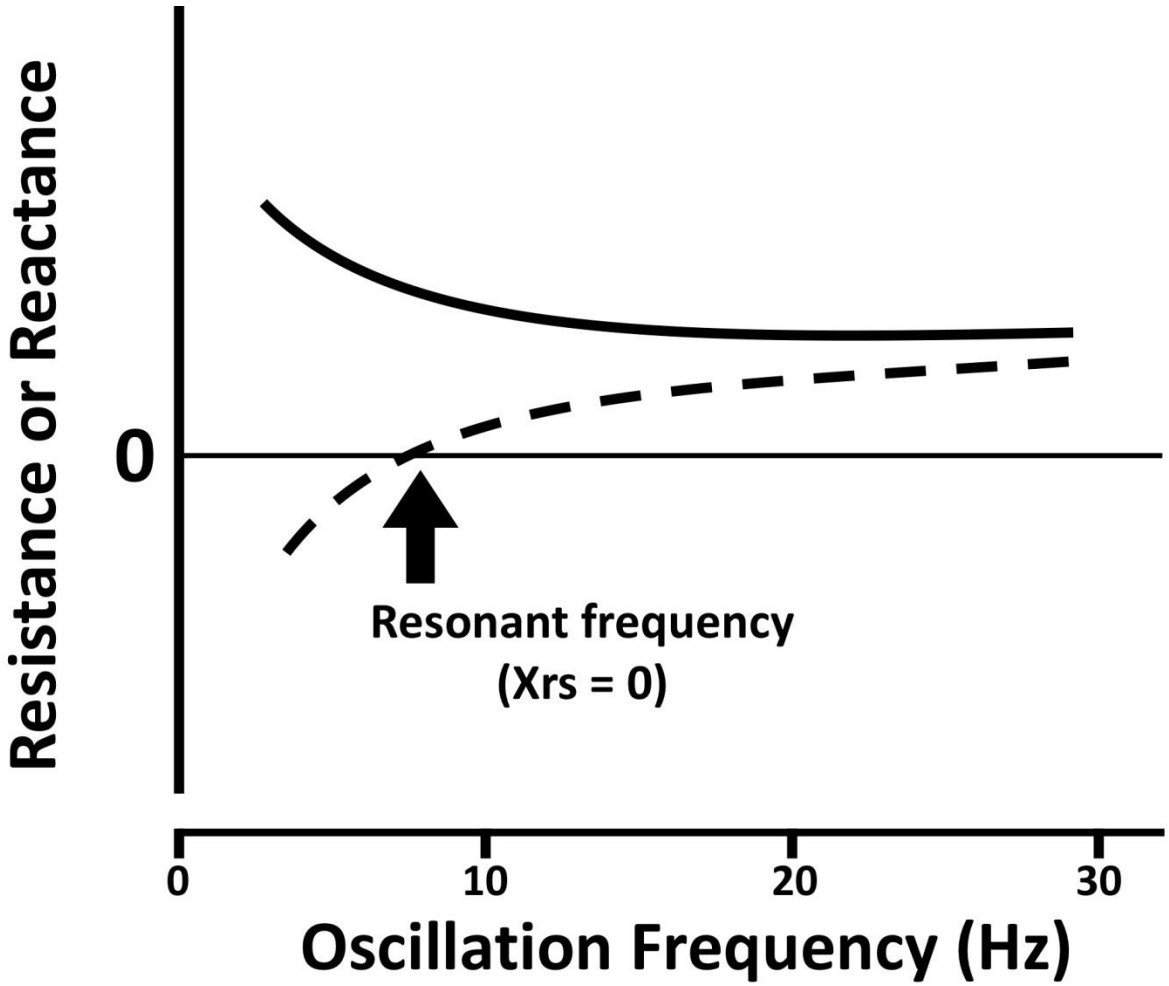
Figure Legends

Figure 1. Diagram of frequency dependence of resistance (solid line) and of reactance (dashed line). Resonant frequency is the frequency at which reactance is 0.

Figure 2a and Figure 2b. Illustrative example of a oscillometry PFT report. Note that the oscillometry parameters included in a report should be determined by end-users. NB: The parameters in this example report are *not* a recommendation of which ones to report.


Resistance or Reactance
0
Resonant frequency
(Xrs = 0)
0
10
20
30
Oscillation Frequency (Hz)

DEPARTMENT:
HOSPITAL:

PATIENT DETAILS:

Name:	Height (cm)	Physician:
Sex:	Weight (Kg)	Technician:
DOB:	BMI:	Smoking history:
Age:	Ethnicity:	
Date of testing:	Time of testing:	

Forced Oscillatory Mechanics (hPa/l/s or cmH2O/l/s)

	Predicted	LLN	ULN	% of predicted	Baseline	Z Score	Post BD	Z Score	Absolute change	% Change
Rrs5										
Rrs5(insp)										
Rrs11										
Rrs19										
Rrs5-19										
Xrs5										
Xrs5(insp)										
Xrs11										
Xrs19										
AX										
Fres										
Tidal vol: pre-BD:				post-BD:		Resp rate: pre-BD:			post-BD:	

Reference values are those of XX et al and of YY et al.

Bronchodilator: (Drug and dose)

A signfiicant change in Rrs with bronchodilator is XX hPa/l/s or cmH2O/l/s or XX% of baseline (reference)

A signfiicant change in Xrs with bronchodilator is XX hPa/l/s or cmH2O/l/s or XX% of baseline (reference)

Respiratory Scientist's/Technician's/Therapist's comments: including number of acquisitions made, how many were used and the coefficient of variation of Rrs5. Any difficulties with testing can be noted here e.g. difficulty with mouth seal, tongue position, cheek support etc.

Graphs of Rrs and Xrs. Graphs should show Rrs and Xrs versus oscillation frequency. 95% confidence intervals would also ideally be shown on the graphs.

Clinical details: (reason for test)
Physician's report:

Technical notes: (this section could be made available offline)

Device manufacturer, model, firmware release number:

Filter model:

Acquisition and Quality Control: (1) minimum number of acquisition - XX of Xsecs , (2) artefact identification by XXX, (3) artefacts were handled by XXXX.

Parameter calculation: average of at least 3 acquisitions of coefficent of variation ≤5% (adults) and 15% (children).

Verification: daily impedance verfication (≤ ±10% or ±0.1hPa/l/s, whichever is greater). Loads used and date and time of last verification.

Signal processing: (Method of impedance calculation, window length, overlap, filtering, ensemble averaging, breath detection method, method of AX calculation.)

Serial values:

Date:	Rrs5 (pre-BD)	Z Score	Rrs5 (post-BD)	Z Score	Xrs5 (pre-BD)	Z Score	Xrs5 (post-BD)	Z Score

Tables

Table 1. Summary of technical recommendations and clinical testing of oscillometry.

Technical recommendations		Section
1	New test loads should be developed: a dynamic test load that simulates patient breathing and a static load that includes elastic and inertive components.	4.2
2	Verifications should be performed daily and publications should report the input frequencies at which verifications are performed, the resistive loads used and the acceptable tolerances. The recommended tolerance for the verification is ≤ ±10% or ±0.1hPa.s.L^{-1}, whichever is greater. The test loads should cover the range of Zrs encountered in normal oscillometry use. For adults being around 15 hPa.s.L^{-1} and for children around 40 hPa.s.L^{-1}.	4.2
3	Details on signal processing for generation of impedance indices, and their validations, should be published or be made freely available from the relevant laboratories, in references and from device manufacturers.	5
4	Coherence should not be used to exclude data points. There are a number of quality control methods that can be used which should be formalised and disclosed by laboratories, in publications and from device manufacturers.	7.2
Clinical testing		
1	Reference values and cut-offs for bronchial challenge tests be assessed for the local population which would also be oscillometry device specific.	9.2
2	Ensure acquisition of sufficient, artefact free replicates, at the time of testing. Thirty second acquisitions are recommended for adults, which allows recording over at least 3 breaths. Sixteen second acquisitions are recommended for children <12 years of age. The coefficient of variation between replicates is suggested to be ≤15% for children and ≤10% for adults.	6.1
3	Oscillometry testing should precede tests requiring deep breaths (e.g. exhaled nitric oxide, spirometry, diffusing capacity) and allow a standardised length of time during which deep breaths are withheld, before performing oscillometry.	6.3
4.	The recommended thresholds for positive bronchodilator responses in both children and adults is -40% in Rrs5, +50% in Xrs5 and -80% in AX. Z-scores are recommended for future definition of a significant response,	9.1

	which will require data of bronchodilator responses in healthy populations.	
4	Patient acquisition protocols e.g. duration of recording, replicates, should be reported in the laboratory reports and research publications.	8

Table 2. Main differences between current and previous ERS technical standards for oscillometry[1].

New/updated technical recommendations and standards	
1.	The ideal forcing frequencies when applied to spontaneous breathing is ≥4 Hz (changed from ≥2 Hz)
2	Not using coherence function for quality control and use of CoV ≤10% in adults and ≤15% in children
3.	The data supporting the thresholds that define bronchodilator responsiveness by oscillometry have been updated (not defined in 2003). The recommended thresholds for both children and adults is -40% in Rrs5, +50% in Xrs5 and -80% in AX. Z-scores are recommended for future definition of a significant response.
4.	For manufacturers (commercial and non-commercial) to report device accuracy for measuring test loads
5.	Test loads would ideally include inertive and elastic components
6.	Report testing procedures and protocols, and quality control parameters in clinical laboratory reports and in research papers
7.	Oscillometry should be performed before tests which require a deep breath e.g. spirometry, exhaled nitric oxide, and after a standardised period during which deep breaths are withheld. The order of tests and period of withholding deep breaths should be reported.
8.	Modern analysis tools allow removal of breaths entire breaths affected by artefact, so that an acquisition may remain technically acceptable, as long as there are at least 3 breaths remaining in that acquisition
9.	Reference papers (Table E1) has been updated. In adults, 2/6 were retained and 5 newer reference papers were added. In children, 2/9 were retained and 10 newer reference papers for school-aged children and 1 for preschool-aged children were added.
10.	Threshold values for bronchial challenge testing should be developed for local populations which would be device specific.

Recommendations that were not included in the current Document	
1.	Input peak pressure upper limit (still valid)
2.	Use of 4-30 Hz frequency range to explore frequency dependence of Zrs (still valid)
3.	Clinical application in respiratory diseases and potential for differentiating disease from non-disease (not within the scope of the current Taskforce)

Table 3. Studies comparing cut-offs during bronchial challenge testing using Oscillometry vs spirometry.

Reference	**Population**	Oscillometry device	Oscillometry cut-off
Paediatric studies			
Lebecque 1987 [147]	17 children with AHR & 14 non-AHR	Oscillaire	50% increase R6 with histamine
Bouaziz 1996 [148]	38 asthmatic children	Pulmosfor 4-32Hz or 6 & 12Hz	70% change R12 and 1 hPa/l/s decrease in X12 with methacholine
Jee 2010 [149]	50 asthmatic pre-school children & 41 children with cough	IOS	80% decrease in X5 with methacholine
Bailly 2011[150]	227 children with suspected asthma	IOS	50% decrease X5 with methacholine
Schulze 2012 [151]	48 children	IOS	45% increase in R5 or 0.69 kPa/L/s decrease in X5 to methacholine
Adult studies			
van Noord 1989 [152]	53 adults	Custom device	47% increase in R5 detecting 15% decrease in FEV1 to histamine
Hsuie 1993 [153]	141 adults (asthma, cough, psychogenic dyspnoea and healthy)	?	?
J. Pairon 1994 [154]	119 adults with normal FEV1 from occupational screening.	Custom device	65% increase in R0 with methacholine
A.B. Bohadana 1999 [27]	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 [30]	52 asthmatic and 15 healthy adults	Custom device	27% decrease in Grs6 or 0.93 cm H_2O/l/s

			decrease in X6 with mannitol

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

Table 4. Key information that should be reported on signal processing in oscillometry measurements

Key information (see Section E1)
Method for impedance calculation
Window length, overlap
Filtering (low and band pass) specifications
Ensemble averaging details
Breath detection method
Quality control and rejection criteria

Table 5. Minimum instructions to be provided to subjects prior to oscillometry acquisition.

Explain to the patient the duration of a single acquisition and the number of replicates that are likely to be recorded
Describe the nature of the sensations generated by the pressure oscillations, e.g. that they will sense a gentle 'vibration' or 'fluttering' in their mouth and cheset during the measurement. A practice run before data acquisition may be useful, particularly in young children.
Encouragement to be relaxed and to 'breathe as normal'
Explain that an initial brief period of observation while breathing on the mouthpiece will occur before the oscillation starts, which is to ensure breathing is normal and stable before the acquisition starts
Correct head position – ask the subject to have an upright posture with a very slight 'chin-up' position if seated (which should be the case for most clinical tests in adults and young children)
Avoiding swallowing
Instruct and demonstrate how the teeth and lips should grip and maintain a firm seal on the mouthpiece to avoid leaks.
Ask the patient to keep the tongue relaxed and below the mouthpiece and do not block the orifice
Instruct and demonstrate if necessary, support of the cheeks with the palm and fingers, and of the floor of the mouth with the thumb positioned below the chin. In children, cheek support must be done by staff or parents.

Table 6. Measurement details for reporting

Device name, model, software version and manufacturer
Input signal frequencies
Duration of individual recordings
Number of repeats
Definition of how impedance values were derived e.g. mean of entire recordings, whole breaths only, inspiratory or expiratory.
Description of breathing protocols e.g. specific breathing maneuvers, tidal breathing, volume history
Use of nose-clip, and method of cheek support.
Head and body position

Table 7: Oscillometry measures to report relating to quality control (see Sections 7 and 8).

Strategies for artefact removal that were used, e.g. visual checks, statistical filtering, whether individual window vs complete breath removal vs entire replicate were rejected
Measurement duration
Number replicate measurements used
Within session CoV and the cut-off used to define acceptability

Technical Standards for Oscillometry – Online Supplement

Gregory G. King[1], Jason Bates[2], Kenneth I. Berger[3], Peter Calverley[4], Pedro L. de Melo[5], Raffaele L. Dellacà[6], Ramon Farré[7], Graham L. Hall[8], Iulia Ioan[9], Charlie Irvin[2], David W. Kaczka[10], David A. Kaminsky[2], Hajime Kurosawa[11], Enrico Lombardi[12], Geoffrey N. Maksym[13], François Marchal[9], Beno W. Oppenheimer[3], Shannon J. Simpson[8], Cindy Thamrin[1], Maarten van den Berge[14] and Ellie Oostveen[15].

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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 (200 μg)	Rrs6: -32%, Xrs8: +50%, AX: -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 & 12Hz	70% change R12 and 1 $hPa.s.L^{-1}$ decrease 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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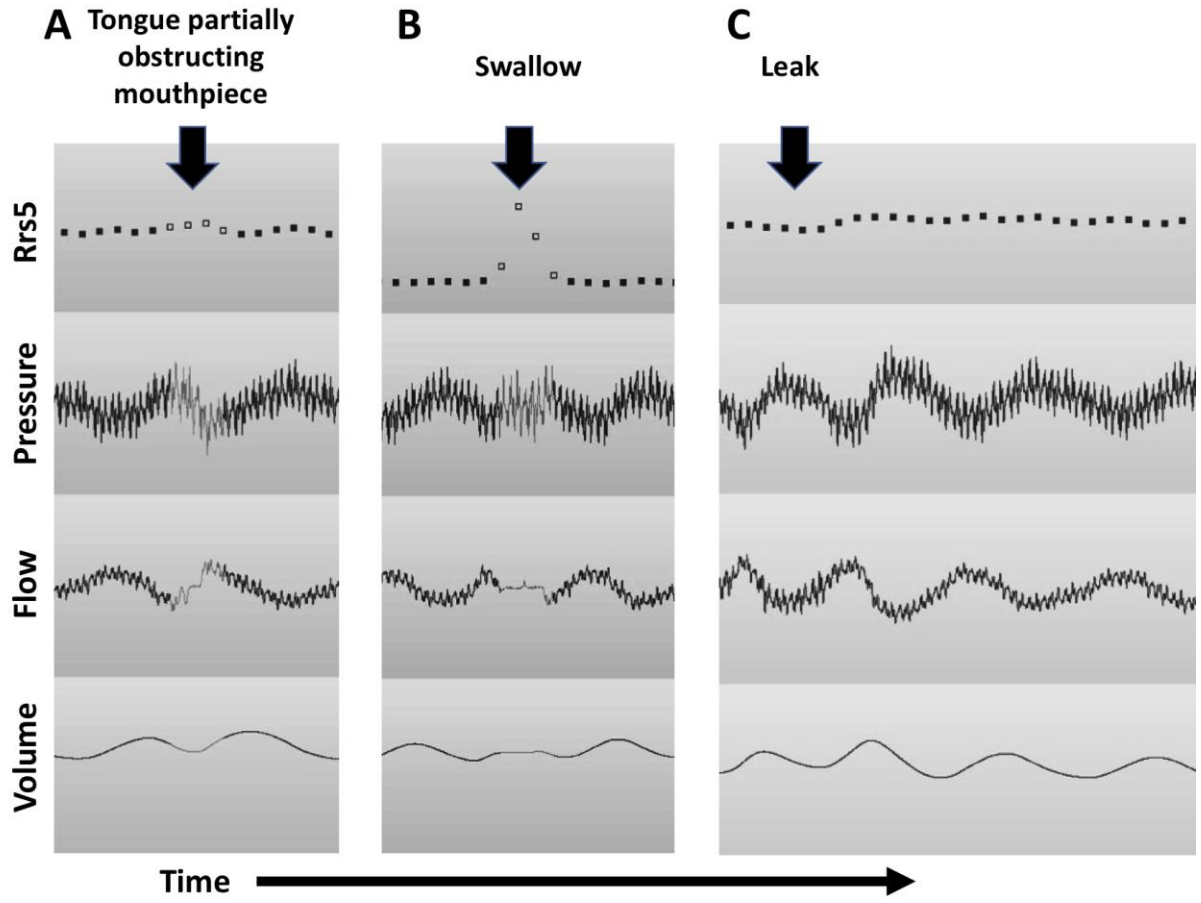
A
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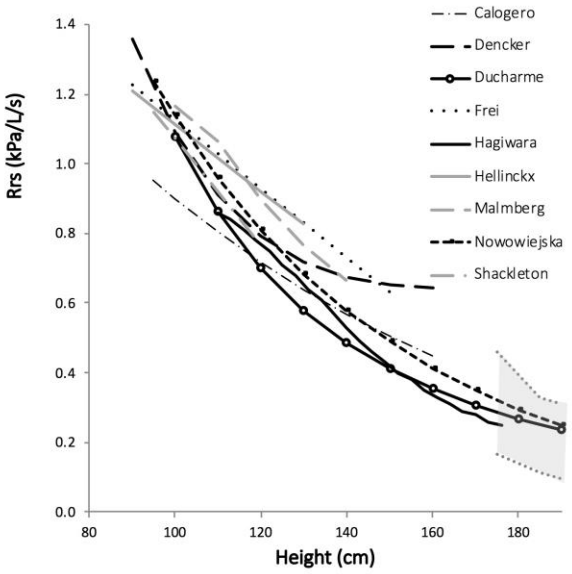
Rrs (kPa/L/s)
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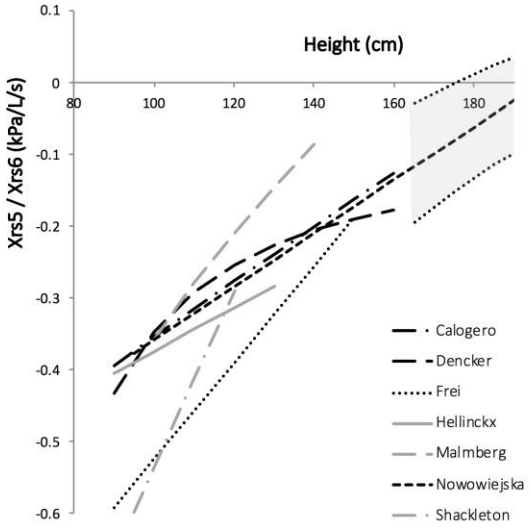
Xrs5 / Xrs6 (kPa/L/s)
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160
180
Height (cm)
Calogero
Dencker
Frei
Hellinckx
Malmberg
Nowowiejska
Shackleton